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Perceptions of Social Isolation and Social Support in Alpha-1 Antitrypsin Deficiency and Sarcoidosis: Results of a Mixed-Methods Study

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Perceptions of Social Isolation and Social Support in Alpha-1 Antitrypsin Deficiency and Sarcoidosis: Results of a Mixed-Methods Study

By

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ABSTRACT

Purpose

The purpose of this dissertation was to explore perceptions of social isolation and social support in individuals with one of two rare lung conditions, alpha-1 antitrypsin deficiency (AATD) or sarcoidosis. First, a dimensional concept analysis was conducted to identify key factors contributing to the phenomenon of social isolation. Next, an integrative review of existing instruments to measure social isolation was conducted to identify the most appropriate instrument for the study. Finally, a mixed-methods study was conducted to explore these phenomena in the two populations of interest.

Problem

Many rare diseases are chronic, complex and associated with other disabilities (M. Anderson, E. Elliott, & Y. Zurynski, 2013). Over the past three decades, social isolation has been shown to be predictive of mortality and morbidity in both general populations (Brummett et al., 2001; House, 2001; House, Umberson, & Landis, 1988) and in populations with chronic conditions (Berkman, 1995; Berkman & Syme, 1979). A review of the research literature revealed no published studies that explored this phenomenon in rare disease populations, and specifically, in rare lung diseases (Flavin, 2015a).

The specific aims of the dissertation were:

- **Aim 1:** To examine the phenomenon of social isolation through the lens of dimensional concept analysis

- **Aim 2:** To conduct an integrative review of instruments designed to measure perceived social isolation
- **Aim 3:** To explore the perceptions of social isolation and social support in individuals with sarcoidosis or alpha-1 antitrypsin deficiency in a pilot study using a convergent parallel mixed methods design.

Design

A convergent parallel mixed methods study design, informed by social network theory (Heaney and Israel, 2008) guided the collection of parallel quantitative and qualitative data streams.

Findings

In the mixed-methods study, there were statistically significant differences in the Friendship Scale, MOS-SSS emotional support, positive social interaction and total scores between the alpha-1 and sarcoidosis groups, with higher scores observed in those with alpha-1 (indicating more social connectedness and perceived support). Sarcoidosis-affected individuals who participated in support groups reported more social isolation as reflected in the Friendship Scale scores than those who did not participate in support groups (p=0.04). This was not the case in the AATD population, where access to support did not significantly alter isolation scores. Content analysis revealed six themes: Self-reflection, building connections, activities, knowledge, relationships and physical/psychological impact. Triangulation revealed that scores on both instrument measures were supported by the qualitative data in both groups.

Conclusions

Individuals with rare conditions do perceive varying levels of social isolation and low social support that may not directly correlate with their reported access to support. The impact of these phenomena is multi-layered and influenced by one's support network. These findings merit further exploration in the form of larger studies that include more geographically and demographically diverse populations. Findings from this dissertation are significant for nurses and other health care providers because they allow for a more complete understanding of the issues confronted by individuals and their family members who are faced with either one of these conditions.

Keywords: *social isolation, social support, alpha-1 antitrypsin deficiency, sarcoidosis, rare disease, mixed-methods*

1. INTRODUCTION

1.1. Overview of Dissertation

Many rare diseases are chronic, complex and associated with physical, intellectual or neurological disabilities (Anderson, Elliott, & Zurynski, 2013). Over the past three decades, social isolation has been shown to be predictive of mortality and morbidity in the general population (Brummett et al., 2001; House, 2001; House, Umberson, & Landis, 1988) and in populations with chronic conditions (Berkman, 1995; Berkman & Syme, 1979). A review of the research literature revealed no published studies that explored this phenomenon in rare disease populations, and specifically, in rare lung diseases (Flavin, 2015a). Despite the high number of individuals affected by rare diseases as a whole, rare disease patients report often feeling isolated and unable to get the information and support needed (Colledge & Solly, 2012). This dissertation focused on investigation of social isolation in a subset of individuals with rare lung diseases, sarcoidosis and alpha-1 antitrypsin deficiency (AATD).

The specific aims of the dissertation were:

- **Aim 1:** To examine the phenomenon of social isolation through the lens of dimensional concept analysis, identifying the qualities of the concept of social isolation and exploring the relationships between the qualities in order to define the essential meanings associated with social isolation
- **Aim 2:** To conduct an integrative review of instruments designed to measure perceived social isolation and examine the qualities of each, in order to choose the

most appropriate instrument(s) to measure the construct in the populations of interest.

- **Aim 3:** To explore the perceptions of social isolation and social support in individuals with sarcoidosis or alpha-1 antitrypsin deficiency in a pilot study using a convergent parallel mixed methods design. We also sought to gain preliminary understanding of the effects of participation in support groups in these individuals.

The overall objective of this study was to gain insight into perceptions of the social impact, particularly social isolation and social support, and its consequences as experienced by individuals with AATD and sarcoidosis. The overarching question driving this proposal was: *To what extent do individuals with the rare lung diseases of AATD and sarcoidosis perceive the social impact and consequences of living with these diseases as documented via participant self-report and as measured by the Friendship Scale and the Medical Outcomes Study – Social Support Survey (MOS-SSS)?* The results of this study provide a framework to design future larger studies that could be used to validate the findings and ultimately, to develop and test interventions that could ameliorate these perceptions. The long-term goal of this research trajectory is to refine hypotheses related to the perceived effect of living with a rare disease on social interactions and support experienced by individuals with AATD and sarcoidosis and to inform future intervention development.

2. BACKGROUND AND PROBLEM STATEMENT

An estimated 10% of Americans live with a diagnosis of one of the 6,000 to 8,000 known rare diseases (Griggs et al., 2009). More specifically, recognition of the

importance of research into rare lung diseases has been growing (Gupta, Bayoumi, & Faughnan, 2011). The experience of living with a rare condition is complex and can significantly affect the individual's quality of life (Cohen & Biesecker, 2010). Current clinical practice views the management of rare diseases primarily from the biomedical approach, seeking to manage clinical physiologic symptoms (Budych, Helms, & Schulz, 2012). Less attention has been given to the psychosocial management of the impact of these conditions. As these patients may have significant needs and barriers to access to care (such as geographical distance from an expert provider), alternative interventions to ameliorate the negative psychosocial aspects of these conditions must be considered. In rare diseases, there is an increasing importance and presence of the patient as an active participant in their disease management and decisions (Aujoulat, Young, & Salmon, 2012; Aymé, Kole, & Groft; Black & Baker, 2011; Johnson, Kirschenbaum, Mason, & Rush, 2005; Polich, 2012). As such, this patient-centric focus calls for a parallel patient-centered research approach, such as interpretive phenomenological analysis (IPA)(Smith, Michie, Stephenson, & Quarrell, 2002). Before designing interventions, it is prudent to seek the voice of the patient.

Many studies have adopted a population-based approach to rare diseases, but the patients' viewpoint on having such a disorder has remained largely understudied (Huyard, 2009). These patients can experience a myriad of psychosocial effects, including social stigma, lack of social support, and perceptions of social isolation. Over the past decade, social isolation has garnered increased attention as an integral component of health (World Health Organization, 2002) and the link between social isolation and health was one focus of the National Research Council's (2001) interest

in integrative health. In a recent review, Cacioppo & Cacioppo (2014) observed the negative impact that social isolation can have on executive functioning, sleep, and mental and physical well-being, ultimately resulting in higher rates of morbidity and mortality in various populations (Cacioppo & Hawkley, 2003; Cacioppo, Hawkley, Norman, & Berntson, 2011; Cornwell & Waite, 2009; Steptoe, Shankar, Demakakos, & Wardle, 2013). Despite confirmation of perceived social isolation in Internet chat rooms, support group meetings, and limited studies of rare disease patients (Black & Baker, 2011b; Coulson, 2005; Coulson, Buchanan, & Aubeeluck, 2007; Lasker, Sogolow, & Sharim, 2005), there is a need for formal study of this phenomenon.

This dissertation is significant because the qualitative component of this study affords a novel opportunity to gather, firsthand, patient perspectives on the social impact of rare disease to supplement baseline quantitative data. This mixed methods approach can be utilized to guide larger studies in more diverse populations of rare disease patients, with the goal of developing and testing interventions that can enhance social support and ameliorate the condition of social isolation. This research is also aligned with the mission of the NINR, and specifically, the need to "develop strategies to assist individuals and their caregivers in managing chronic illness, including analyses of caregiver burden and cost-effectiveness" (National Institute of Nursing Research, 2011, p. 15). This work provides preliminary insights into the experiences of these individuals, and may serve as a reference point to develop strategies to address the management of the social isolation component of these rare, chronic diseases. Findings from this study may also be utilized to explore perceived social isolation and social support in other rare disease populations.

3. GAPS IN KNOWLEDGE

Few published studies have explored the experiences of living with a rare disease; no published studies were identified that explored social isolation in rare lung diseases such as AATD or sarcoidosis. Two studies conducted in the rare disease of scleroderma identified social isolation as a phenomenon experienced by these individuals. Joachim & Acorn (2003) conducted a phenomenologic study to investigate the perspective of living with scleroderma and identified persistent themes of stigma and isolation. In their study of scleroderma patients, Cinar and colleagues (2012) found similar themes, including social isolation. Henderson and colleagues (2009) investigated the general psychosocial impact of living with Niemann Pick disease Type B, a rare lysosomal storage disorder; they also observed that those patients reported feelings of social isolation. McGarvey and Hart (2008) surveyed over 200 general practitioners in Ireland; they found that 72% of GPs agreed that having a rare disorder gives rise to additional family problems and 28% felt that rare disorders can result in feelings of isolation. No published studies have focused solely on the phenomenon of perceived social isolation in individuals living with rare diseases.

Similar results were found when seeking to identify published studies on perceived social support in these conditions. No published studies were identified that explored perceived social support in sarcoidosis or AATD, although Hoth and colleagues (2014) investigated 400 individuals with AATD and found that participation in support groups was associated with less ambiguity surrounding the disease. A statistically significant impact on ambiguity was found in those individuals who attended three or

more support groups in the prior year compared with individuals who reported no such participation (b=−3.31, SE=1.29, p=0.010)

4. DESIGN AND METHOD

Both the exploration of the concept of social isolation via dimensional concept analysis, as well as the integrative review of instruments to measure the concept provided a framework from which to design the dissertation study. The parallel convergent mixed-methods design of the study was informed by Creswell & Plano Clark (2011). A quantitative descriptive approach required participants' completion of the Friendship Scale (Hawthorne, 2006), a six-item Guttman scale that measures social isolation and the Medical Outcomes Study: Social Support Survey (MOS-SSS), a 19-item version instrument that measures perceived availability of social support. Semi-structured, individual interviews were conducted to describe individuals' perceptions and experiences of social support, relationships with others, and preferences for support strategies. This descriptive approach provided for a comprehensive summary of the experiences of social isolation and social support in the participants' own terms (Sandelowski, 2000). A convergent design facilitated the collection, analysis and subsequent merging of two independent data streams in a single phase (Creswell & Plano Clark, 2011). After merging, divergence, convergence and other relationships were explored.

5. KEY CONCEPTS/TERMS AND DEFINITIONS

There are two main concepts explored in this dissertation that merit presentation as a component of the dissertation introduction, social isolation and social support.

5.1. Social Isolation

There have been many attempts to operationalize a working definition of social isolation. The concept of social isolation was first discussed at length in the literature in the 1970s and 1980s. Despite this rather lengthy history, social isolation continues to be defined inconsistently and/or used as an adjective describing very low levels of social support, or limited or lacking social networks (Nicholson, 2009). Warren (1993) offered four criteria as defining characteristics of the phenomena. The first, *stigmatized environment*, implies that a person has been designated as different from other persons, they perceive this difference and they are hesitant, unwilling, or do not know how to participate in social interactions with others. This same characteristic was also noted by Joachim and Acorn (2003) in their focus group interviews conducted with individuals suffering from the rare disease of scleroderma. The second criterion is that of *societal indifference*, where the person perceives that they are lonely, and they lack enduring or meaningful relationships with others. The third criterion has to do with *personal-societal disconnection*, which implies that society rejects and alienates the stigmatized person by denying them access to satisfying social situations and interactions. Last is the criterion of *personal powerlessness* where the stigmatized person buys into their own perception that society has rejected them; they feel as if they have no control and others possess all control.

The results of the dimensional analysis conducted as a component of this dissertation suggest that there are multiple factors related to the concept of social isolation. Using Schatzman's approach, the dimensions of perspective, context, condition, process and consequences were explored as they relate to this concept. The

first, perspective, is that of *limited or low social networks* as well as the *lack of personal relationships* and is the central organizing standpoint of individuals experiencing perceived social isolation. The second component, that of context, suggests that the condition occurs most often in *community-dwelling older adults*. The conditions that often foster social isolation are that of a *stigmatized environment* as well as the disease *condition*. The processes that can affect social isolation are *peer counseling, support groups, enhancement of family networks, or internet-based support* (Biordi & Nicholson, 2009; Cudney, Butler, Weinert, & Sullivan, 2002, Holley, 2007; Weinert, Cudney, & Hill, 2008). These findings are congruous with Nicholson's (2009) proposed definition of social isolation which suggests that social isolation is a state in which the individual lacks a sense of belonging socially, lacks engagement with others, and has a minimal number of social contacts that are deficient in fulfilling and quality relationships. In his concept analysis of social isolation in older adults, Nicholson (2009) suggested that determinants of isolation include "number of contacts, feelings of belonging, fulfilling relationships, engagement with others, and quality of network members" (p. 1349). Killeen (1998) defines social isolation using two different perspectives: "Social isolation with choice is aloneness, while social isolation without choice is loneliness" (p.764). Based on these theories, the working theoretical definition of social isolation is proposed as living without companionship, having low levels of social contact, little social support, feeling separate from others, being an outsider, isolated and suffering loneliness (Hawthorne, 2006).

5.2. Social Support

Attempts at crystallizing a definition of social support in the literature are abundant, and yet, lack of a consensus definition prevails. One theme, however, is generally consistent in that the construct has been studied primarily from three perspectives: network structure, support functions and the nature of relationships. Social support has been defined and measured in various ways (Broadhead et al.1983, Schwarzer & Knoll 2007). However, most definitions of social support refer in some context to Cobb's seminal publication and resulting definition of social support as "the individual belief that one is cared for and loved, esteemed and valued, and belongs to a network of communication and mutual obligations" (Cobb, 1976, p. 300). The chosen instrument, the MOS-SSS reflects these components by its separation and measurement of the domains of emotional/informational support, tangible support, affectionate support, and positive social interaction. Strategies to ameliorate perceptions of social isolation include various types of social support. The need for the assessment and interventions to address social support needs of individuals with rare conditions is illustrated by the European Union Committee of Experts on Rare Diseases (EUCERD) in their investigation into the social support needs of individuals with rare diseases (EUCERD & Diseases, 2012). While the goal of this study is not to investigate the effect of interventions, the assessment of the perceptions of social support is important to consider.

6. THEORETICAL FRAMEWORK

The social network theory proposed by Heaney and Israel (2008) is one that is most applicable to this work. The model depicts social networks and social support as the starting point or initiator of a causal flow toward health outcomes. The depiction of

this model provides a succinct illustration of how social support and social networks are intertwined.

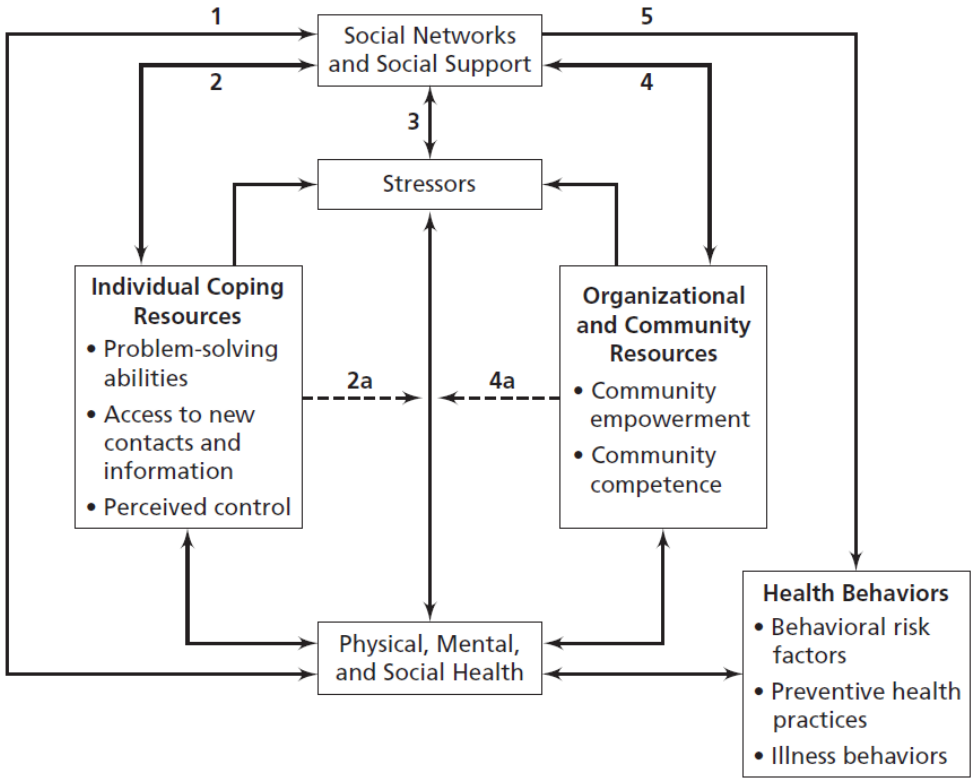

Figure 1: Conceptual Model for the Relationship of Social Networks and Social Support to Health

As suggested by Heaney and Israel (2008, p. 189), an understanding of the impact of social relationships on health status, health behaviors, and health decision making can contribute to the design of effective interventions for promoting health. In the case of rare diseases, community empowerment is evident in the alpha-1 population, and less so (in an organized fashion) in the sarcoidosis population. As illustrated in Figure 1, Pathway 1 denotes the direct effect of social networks and social support on health. By meeting human needs for companionship, a sense of belonging, and reassurance of one's worth as a person, supportive ties may enhance well-being and health, regardless of stress

levels (Berkman and Glass, 2000). This was also observed in the work of Brummett et al (2001), Berkman and Syme (1979) and House and colleagues (1988). Pathways 2 and 4 represent the effect of social networks and social support on individual coping resources and community resources, respectively. Pathway 3 suggests that social networks and social support may influence the frequency and duration of exposure to stressors. Pathway 5 reflects the potential effects of social networks and social support on health behaviors. Through social support and such networks, healthy behaviors, adherence to prescribed regimens and other health-seeking behaviors can be enhanced. In applying this to the rare disease populations, it is clear that further study is needed, in order to draw correlations between specific behaviors and health outcomes, as well as identification of stressors that may be specific to these groups. It is hoped that the results of this dissertation can provide a sound foundation and framework from which other work can flourish.

7. BRIEF OVERVIEW OF MANUSCRIPTS

The *first manuscript* of this dissertation presents a dimensional concept analysis of the phenomenon of social isolation (Flavin, 2015a). A concept analysis guides dissection and examination of key components of the phenomenon under consideration, affording a multifaceted lens with which to view the attributes of the construct. Schatzman's method of dimensional analysis (1991) is particularly suited to exploration of social isolation. Dimensional analysis (DA) is a method focused on identifying the various factors that are involved with a phenomenon (Hobbs, 2009), and can be particularly useful when evaluating an unclear or potentially ambiguous concept (Kools, McCarthy, Durham, & Robrecht, 1996). Dimensional analysis offers an approach to the

understanding of social isolation through its social construction and examination of differences across perspectives and contexts (Udlis, 2011). Schatzman's methodology directed the investigator to explore the dimensions of perspective, context, condition, process and consequences as they relate to social isolation and categorized according to best fit. By definition, the central theme of social isolation was the perception of having limited or low social networks as well a lack of personal relationships. The results of the concept analysis as a whole are presented in the published manuscript entitled "Social Isolation and its Applicability to Persons with Sarcoidosis and Alpha-1 Antitrypsin Deficiency: A Dimensional Concept Analysis" (Flavin, 2015a). The results of the dimensional analysis provided a more robust understanding of the various components that contribute to the phenomenon of social isolation.

The *second manuscript* of this dissertation presents the results of an integrative review of the various instruments available to measure social isolation. This paper, entitled "Measurements of social isolation and social support for rare lung disease patients: An integrative review" (Flavin, 2015b) presented the results of a review of eight instruments that purported to measure the construct of social isolation. From that review, the Friendship Scale and the UCLA Loneliness Scale were identified as those instruments with acceptable psychometrics and that would be suitable for pilot use in the populations of interest.

The *third manuscript* of the dissertation presents the results of the pilot study, which used a mixed-methods approach to explore the perceptions of social isolation and social support in individuals with sarcoidosis or alpha-1 antitrypsin deficiency**.**

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MANUSCRIPTS

1.1. Social Isolation and its Applicability to Persons with Sarcoidosis and Alpha-1 Antitrypsin Deficiency: A Dimensional Concept Analysis

Special Article

Social Isolation and its Applicability to Persons with Sarcoidosis and Alpha-1 Antitrypsin Deficiency: A Dimensional Concept Analysis

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Abstract

Background: Social isolation is a phenomenon that is a major health problem among various individuals. The chronically ill and other marginalized populations suffering from the stigma of a health condition are especially vulnerable. No studies to date have examined this meaning of this concept in rare lung diseases, including sarcoidosis or alpha-1 antitrypsin deficiency.
Aim: The aim of this paper is to gain further insight into the concept of social isolation and how it might apply to sarcoidosis and alpha-1 antitrypsin deficiency. A dimensional analysis was undertaken to examine the various uses of the concept. Dimensional analysis is a method of concept analysis that is particularly useful in exploring a concept such as social isolation that may be somewhat ambiguous.
Methodology: The analysis includes 15 papers from 15 research studies from the disciplines of nursing, social sciences, psychology, palliative care and medicine. Caron and Bowers' dimensional analysis approach informed the analysis, and coding of the perspective, context, conditions, process, and consequences of social isolation was performed
Results: The perception of having limited or low social networks is the central organizing standpoint of individuals experiencing perceived social isolation. Social isolation often occurs in adults as the result of a chronic illness. Individuals who exist in a stigmatized environment are at risk. Individuals at risk for social isolation may benefit from such interventions as peer counseling, support groups or internet-based support. Finally, clinicians should be cognizant of the deleterious effects of social isolation, including increased morbidity and mortality.
Conclusions: Social isolation remains an ambiguous concept which has garnered considerable attention within the last decade. The type of and magnitude of social isolation can be dependent upon the context, the condition, and the tools to facilitate management of the phenomenon. Specific to rare lung diseases, further research is warranted and timely.

Key Words: social isolation, sarcoidosis, Alpha-1 antitrypsin deficiency, dimensional concept analysis

Introduction

The question of whether human beings can thrive apart from others has been pondered for centuries. John Donne (1572-1631) wrote "No man is an island…entire of itself" in his Meditation XVII (Donne, 2001). Conversely, the philosophy of existentialism suggests that human beings are essentially alone in the world (Biordi & Nicholson, 2009). According to the Oxford English Dictionary, isolation is defined as "the action of isolating; the fact or condition of being isolated or standing alone; separation from other things or persons; solitariness" (2012). The term is further refined as "the separation of a person or thing from its normal environment or context, with for purposes of experiment and study or as a result of its being, for some reason, set apart" (OED, 2012). The term first appeared, according to the OED, in 1833, in the work *Charmed Sea*

by H. Martineau (OED, 2012). In the psychological and sociological context, the term has evolved from one of its original appearances in 1890 in the work of C.L. Morgan's *Animal and Life Intelligence*: "We may call the process by which we select a certain quality, and consider it by itself to the neglect of other qualities, *isolation"* to a more robust definition in *The Modern Dictionary of Sociology (Theodorson & Theodorson, 1970)* where the authors suggested that prolonged isolation of an individual from satisfying social involvement with others usually leads to or is a result of a mental disorder". There have been no published studies to date of the exploration of the phenomenon in sarcoidosis,alpha-1 antiryspin deficiency or rare disease groups.

There are few, if any, colloquial uses of the term *social isolation.* In the current literature, the concept has multiple meanings. Carpenito-Moyet (2006) succinctly defined social isolation as "the state in which the individual or group expresses a need or desire for contact with others but is unable to make that contact". Others have sought to crystallize a more refined definition of social isolation. In his concept analysis of social isolation in older adults, Nicholson (2009) suggested that determinants of isolation include "number of contacts, feelings of belonging, fulfilling relationships, engagement with others, and quality of network members" (p. 1349). Killeen (1998) defines social isolation using two different perspectives: "Social isolation with choice is aloneness, while social isolation without choice is loneliness". Biordi and Nicholson (2009) state that loneliness should be considered the subjective emotional state of the individual, whereas social isolation is the objective state of deprivation of social contact and content. This is in contrast to Carpenito's belief that social isolation is more of a subjective state (Carpenito-Moyet, 2006). This overview demonstrates that the concept has not been uniformly defined and consensus agreement is elusive.

One approach to elucidating the salient features of this multidimensional phenomenon is through concept analysis. Concept analysis presents strategies necessary to dissect key components of the phenomenon under consideration, affording a multifaceted lens with which to view the attributes of the construct. This then begs the question of which approach to use for a given phenomenon of interest. Schatzman's method of dimensional analysis (1991) is particularly suited to exploration of social isolation. Dimensional analysis offers an approach to the understanding of social isolation through its social construction and examination of differences across perspectives and contexts (Udlis, 2011). Using the dimensional method, the purpose of this analysis is to explore the concept of social isolation within the context of the various dimensions identified through the literature. Since repeated and extensive searches of the literature revealed no publications of social isolation in the context of sarcoidosis, the identified populations were broadened to include chronic disease limited to adult populations.

Social isolation in the context of sarcoidosis and alpha-1 antitrypsin deficiency

Social isolation is gaining increased attention as an integral component of health (World Health Organization, 2002). Social isolation has been demonstrated to be directly correlated to morbidity and mortality (House, 2001; House, Landis, & Umberson, 1988; House, Umberson, & Landis, 1988; Berkman, 1995; Berkman & Syme, 1979). There is little work done within the context of rare lung diseases and no published literature identified regarding any investigation into social isolation in the context of sarcoidosis or alpha-1 antitrypsin deficiency.

Sarcoidosis is a rare granulomatous disease of unknown etiology. Many organ systems can be affected, although lung involvement is most common, occurring in greater than 75% of patients (Patterson, et al, 2012). While more than half of patients undergo remission with no significant morbidity, a subset of patients (about 30%) develops chronic disease (Patterson et al., 2012).

Because the disease is rare, there is limited public awareness or support of persons with this condition. Delays in diagnosis and/or misdiagnosis may promote distrust of health care providers and counselors. The combination of these factors can lead to perceptions of social isolation. Young and colleagues (Young, et al,

1997) reinforced the importance of social support in sarcoidosis by suggesting that it is best to refer the patient to a sarcoidosis support group for reassurance and to allay anxiety, reduce stress, and share similar experiences with others.

Ireland and Wilsher (2010) suggest that sarcoidosis patients may have significant psychological distress relating to perception of their disease and that distress is likely underestimated by their clinician. Social withdrawal has been documented as a result of the combination of the disease and the onset of stressful life events (Trombini & Trombini, 2012). The combination of these factors can lead to perceptions of social isolation.

Similarly, alpha-1 antitrypsin deficiency (AATD) is an uncommon genetic disease which that affects approximately 1 in 2,000 to 1 in 5,000 individuals and predisposes to early-onset emphysema and liver disease (Stoller and Aboussouan, 2012). Previous studies have confirmed adverse psychosocial effects related to an AATD diagnosis (Stoller, et al, 1994). Social isolation has been explored in individuals with COPD (Ellison, et al, 2012; Seamark, et al, 2004) but no published studies were identified that investigated social isolation in AATD patients specifically.

Measurement of Social Isolation

Operational definition

There have been many attempts to operationalize a definition of social isolation. Warren (1993) offered four criteria as defining characteristics of the phenomena. The first, *stigmatized environment*, implies that a person has been designated as different from others, they perceive this difference; and is hesitant, unwilling, or unsure of how to participate in interactions with others. This characteristic was also noted by Joachim and Acorn (2003) in their focus group interviews conducted with individuals suffering from scleroderma, another rare disease. The second criterion is that of *societal indifference*, where the person perceives loneliness, or a lack of enduring or meaningful relationships with others. The third criterion is *personal-societal disconnection*, where society rejects and alienates the stigmatized person by denying them access to satisfying social situations.

Last is the criterion of *personal powerlessness* where the stigmatized person believes the perception that society has rejected them; they feel as if they have no control and others possess all control.

Theoretical Framework Considerations

There is a paucity of information in the literature that speaks to conceptual models related to social isolation, rendering the concept persistently ambiguous (Nicholson,2009). Roy's Adaptation Model can guide examination of the concept of social isolation, as it describes the nurse as facilitating an adaptive process to restore health. In the model, individuals are biopsychosocial beings required to adapt to external stimuli (Barone, Roy, & Frederickson, 2008).

Once a stimulus is received (in this case, the diagnosis), it is exhibited in four distinct adaptive models: physiological, self-concept, role function and interdependence (Nicholson, 2009). Of particular interest is the interdependence mode which encompasses the development and maintenance of satisfying relationships with significant others. These relationships are missing in those who are socially isolated.

Refined Definition of Social Isolation

Social isolation is thus defined as a state in which an individual exists, and which is not by choice. Individuals suffering from social isolation lack feelings of belonging, fulfilling relationships, engagement with others, and a lack of support persons. The individual feels stigmatized by their disease, and powerlessness to change their situation.

Dimensional Analysis

The dimensional analysis method will be used to examine the concept of social isolation. Dimensional analysis (DA) is a method focused on identifying all that is involved with a phenomenon (Hobbs, 2009). It can be particularly useful when evaluating an unclear or potentially ambiguous concept (Kools, McCarthy, Durham, & Robrecht, 1996), such as social isolation. It is also particularly useful in the case of the social isolation, where it would be useful to understand how the concept might be socially constructed, and how it may vary across

perspectives and constructs (Caron & Bowers, 2000).

This dimensional analysis will be executed using Schatzman's theory, and sorted via the concept matrix into one of the five dimensions as illustrated by Schatzman: perspective, context, condition, process and consequences (Schatzman, 1991).

Sample and Search Strategy

Whittemore and Knafl (2005) advocate a five-step process as critical for a robust integrative review of the literature. The first two will be discussed here as a segue to presentation of the concept matrix. The first step involves identification of the problem, in this case, the ambiguity of the concept of social isolation. Through previous searches and anecdotal discussions, the concept of social isolation holds different meanings depending upon the context, the population, and the disease state (if any) in which it occurs.

The second step consists of a well-defined and exhaustive search of the literature (Whittemore & Knafl, 2005). The purpose of this search was to review the literature for the purpose of locating papers and other published information (e.g. book chapters) for the most frequently used definitions of social isolation. Examination of papers that had "social isolation" in either the title or the abstract were the primary focus of the search; other papers and works that appeared in the electronic searches were also reviewed for pertinent information. Results from a previous search on methods and instrumentation were utilized as a baseline reference model from which to frame the current search, expanding on concepts and constructs, rather than methods of measurement.

Scientific databases were searched individually, and included MedLINE, CINAHL, and PsycINFO. In addition, GoogleScholar was searched for variations on and of the search terms. Keywords included "social isolation" , "social support", "chronic disease" , "lung disease" "pulmonary disease, "respiratory disease", "sarcoidosis" and "social support", "concept analysis", "dimensional analysis", "evolutionary analysis" and combinations of these terms. Due to the lack of information regarding social isolation as it relates to sarcoidosis, alpha-1 or rare diseases, articles were included regardless of setting or disease state. Studies were further limited to human studies in adults (19+ years of age), written in English, and encompassed the years 1992-2014. This two decade time span was included so as to include any seminal works that may have been published.

The MedLINE database yielded an initial pool of 4791 articles, despite the filters imposed upon the search terms. This pool of publications was reviewed over the course of multiple sessions for appropriateness for inclusion.

The CINAHL database was searched using the same limitations and terms. Publications were excluded from this search if they appeared in a MedLINE search. This search yielded a total of 502 articles. PsycINFO was searched as the third database; a total of 35 articles were obtained for review. Lastly, GoogleScholar was searched for combinations of and variations on the search terms as stated above. This search yielded a total of 86,800 results, which were reviewed in a cursory manner for potential inclusion.

This initial search strategy yielded a total of 92,139 results. Further critical review resulted in a total of 15 articles and one book chapter (which was requested and obtained). The vast majority of these were excluded due to the interchangeable use of the term "loneliness" with "social isolation". Duplicates were excluded, as well as dissertations and theses. In addition, the search term of 'social isolation" resulted in topics related to the biologic sciences (isolation of viruses, bacteria) which were excluded. Following this electronic search for articles, a hand-search of the references of the selected articles was conducted. This search yielded a total of 2 articles, one being a seminal work on mortality as an outcome of isolation, and was included in the review (Berkman & Syme, 1979).

In consideration of information that might be present in the public domain, or in potentially obscure databases or databases not chosen by the author, the search term combinations of 'social isolation AND chronic illness" and "social isolation AND chronic disease" were searched using the Google search engine via the Internet.

The combination of "social isolation and chronic illness" yielded 2,240,000 results while the combination of "social isolation and chronic disease" yielded 3,350,000 results. Although the search was limited to the first twenty pages of these resources, none of the results reviewed yielded additional information or articles included in the review.

A diagram of the search strategy, excluding the basic Google search is presented in Figure 1, Literature Search Strategy. The concept matrix of the published literature is presented in Table 1.

Results

Common themes and dimensions were sorted according to Schatzman's methodology. The dimensions of perspective, context, condition, process and consequences as they relate to social isolation were examined and categorized according to best fit, since some of the findings from the literature overlapped in terms of applying to multiple dimensions.

Perspective is presented first since it frames and organizes the remaining dimensions of the concept (Hobbs, 2009).

Perspective

The perception of having *limited or low social networks* as well as the *lack of personal relationships* is the central organizing standpoint of individuals experiencing perceived social isolation. This was evident in the majority of the papers reviewed. Hawthorne (2006) found that personal relationships were the key correlate of social isolation in his research. Biordi and Nicholson (2009) suggest that when we think of social isolation, we "think first of the affected person, then we immediately consider that individual's relationships" (p. 87), and that the key correlate of social isolation is often viewed as a deprivation in social contacts. Nicholson (2009) defined social isolation as ''a state in which the individual lacks a sense of belonging socially, lacks engagement with others, has a minimal number of social contacts and they are deficient in fulfilling and quality relationships'' (p. 1346). He later found that individuals who have a minimal number of social contexts were at risk for social isolation (Nicholson, 2012). Pedersen, Andersen and Curtis (2012) found that individuals who perceived isolation also reported low levels of social support. Jonsdottir (1998) observed that the inability to reach out and make connections with other people, resulting in isolation, was a prevalent theme in individuals with chronic obstructive pulmonary disease (COPD), another chronic lung disease often stigmatized due to its association with smoking.

Context

A number of the dimensions reviewed in the literature were categorized as contextual, reflective of the environment or setting where the phenomenon occurs and unfolds (Crighton, 2004). Social isolation often occurred in older adults, and as the result of a chronic illness or disability (Biordi & Nicholson, 2009; Cacioppo & Hawkley, 2009; Cornwell & Waite, 2009; Hawthorne, 2006, 2008). None of the literature reviewed addressed social isolation as occurring in an inpatient setting; the phenomenon was addressed in populations of community-dwelling adults (Biordi & Nicholson, 2009; Cacioppo & Hawkley, 2009; Cacioppo, Norris, Decety, Monteleone, & Nusbaum, 2009). The majority of sarcoidosis and alpha-1 patients are treated on an outpatient basis with the exception of exacerbations of the disease, and for those for whom the disease becomes chronic, they are left to grapple with the issues within their community of residence(Baughman et al., 2001)

Condition

Conditions are elements that facilitate, block or shape actions, interactions and consequences within the phenomenon. The specific issues related to the limited or low social networks or the lack of social support are the conditions necessary for social isolation to become a real challenge to the patient. For example, the disease condition (chronic illness) may dictate the ability of the individual to reach out for help when needed. Younger individuals with chronic illnesses such as fibromyalgia were also found to report social isolation, since the individuals were reluctant to reach out for help for fear of being ostracized (Cudney, et al, 2002). Individuals who existed in a stigmatized environment were also found to suffer from social isolation. These stigmatized populations can range from those suffering from addictions, chronic disease,

imprisoned individuals, to those who perceive alienation because of their race or gender (Warren, 1993). Jonsdottir (1998) found this to be the case in COPD patients, where the individuals repeatedly expressed a wish to have others understand their disease. Biordi and Nicholson also echoed a similar sentiment of disenfranchisement when they suggested that one component of social isolation was the loss of place within one's group, or the weakening or diminishing of one's social role. Holley (2007) also found that social isolation can be more pronounced in individuals who have experienced loss of income due to their disease, and pointed out that such loss of income can also have a negative impact on social activities, which become luxuries for those with scarce financial resources, thus magnifying the issue of isolation. For example, in sarcoidosis (or alpha-1), where the affected individual may have been the primary wage earner in the family, this role may be diminished due to the inability to work secondary to the dyspnea that accompanies the illness.(Baughman et al., 2001; Yeager et al., 2005)

Processes

Conditions such as the type of illness influence processes that evolve within the phenomenon of social isolation. These processes are defined as the actions or interactions that occur within the phenomenon (Schatzman, 1991). Individuals experiencing or at risk for social isolation may benefit from such interventions as peer counseling, support groups, enhancement of family networks, or internet-based support (Biordi & Nicholson, 2009; Cudney et al., 2002; Holley, 2007). (Weinert, Cudney, & Hill, 2008). Aladesanmi (2004) suggests that for the primary care clinician, the role of online discussion groups as a source of patient advice is gaining value, and that many patients with chronic medical conditions (including sarcoidosis and alpha-1) participate in these groups.

Consequences

A number of consequences and processes are also consequences of social isolation. One of the most compelling to date is the Alameda study by Berkman and Syme, conducted over 30 years ago. In that study of over 6000 residents, the researchers found that individuals who lacked social and community ties or social networks were more likely to die in the follow-up period than those with more extensive contacts (Berkman & Syme, 1979). In terms of mortality, age-adjusted relative risks for those most isolated when compared to those with the most social contacts were 2.3 for men and 2.8 for women (Berkman & Syme, 1979).

Cacioppo & Hawkley (2003) found that even in young adults, the presence of perceived social isolation had a profound impact on health-related outcomes. In young adults, stress and repair and maintenance were directly correlated to an individual's perceived state of social isolation. The researchers found that perceived social isolation may weaken anabolic processes that serve to repair and maintain physiological functioning and foster recovery from stress (Cacioppo & Hawkley, 2003). In a disease such as sarcoidosis, where auto-immunity is thought to play a role (Planck, Katchar, Eklund, Gripenback, & Grunewald, 2003), the potential impact of management of such isolation cannot go unrecognized.

Limitations

The most obvious limitation was the paucity of literature speaking to the concept of social isolation in chronic lung disease. According to Caron and Bowers (2000), one "critical consideration is that the selection of sources of text should not be determined by the researcher's assumptions" (p. 300), but one cannot completely eliminate bias. Another limitation was the fact that since the concept remains so poorly defined, the interchangeable use of the term 'loneliness" with "social isolation" persisted, and resulted in a search that proved challenging for both reference librarian and author.

Discussion

The results of this analysis reflect varying uses of the concept of social isolation. This may be dependent upon the population that it is used to describe. However, one predominant theme in the literature was that of limited or low social networks, characterized by lack of personal relationships. In additional, the condition was found often in individuals with chronic illness in

a community setting. These individuals were often in a stigmatized environment, and may be a group that benefits from peer support or peer intervention. This preliminary analysis provides evidence for the need for further characterization of the phenomenon from a disease-specific perspective, as well as perhaps as contextual perspective.

Conclusions

Social isolation remains an ambiguous concept which has garnered considerable attention within the last decade. The aim of this analysis was to examine the concept of social isolation through the lens of dimensional analysis. This approach provided for a more precise dissection of dimensions by the examination of various components of the phenomenon across multiple scenarios and perspectives.

Further research examining the concept in the context of rare lung diseases and/or rare diseases is warranted and timely. Based upon the findings of such investigations, pilot projects could be designed that examine best practices for managing the phenomenon.

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1.2. Measurements of Social isolation and Social Support for Rare Lung Diseases: An Integrative Review

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Measurements of social isolation and social support for rare lung disease patients: An integrative review

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Abstract

Social support is an integral component of health. The risk of social isolation and perceptions of minimal support are high for persons living with rare chronic lung diseases such as sarcoidosis or alpha-1 antitrypsin deficiency. The study of social support and isolation requires validated, reliable instruments to quantify their influence. Objectives: The objective of this integrative review is to identify and critically appraise validated, reliable instrumentation to measure social isolation and related concepts in persons with rare lung diseases such as sarcoidosis or alpha-1 antitrypsin deficiency. Design: Integrative review. Methods: A review of the literature was conducted using PubMed, Medline, CINAHL and PsycINFO databases between 1970-2013. Eleven studies were included which encompassed eight instruments. Results: The Friendship Scale and the UCLA Loneliness Scale demonstrate past psychometric performance suggesting future suitability for use in persons with sarcoidosis or alpha-1 antitrypsin deficiency Conclusion: Existing instruments would be suitable for an initial assessment of social isolation and social support in rare lung disease patients. Relevance to clinical practice: As the era of genomics and genetics continues to evolve, it is likely that conditions that were unrecognized previously may be identified as disease conditions. Moreover, simplification of testing for rare genetic conditions is becoming more commonplace, and clinicians may be faced with managing such patients. Knowledge of the potential or actual social impact of such conditions is necessary in order to provide for holistic management of such patients, and simple, existing tools can be useful.

Keywords: Social isolation, loneliness, rare disease, chronic disease

Introduction

An estimated 30 million Americans live with a diagnosis of one of the 6,000 to 8,000 known rare diseases (1) and such conditions affect approximately 30 million individuals in the EU (2). EURORDIS

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(Rare Diseases Europe) has identified the need to address the social aspects of the rare diseases as one component of living well within the context of a rare condition (3). Such social aspects include, but are not limited to, social support, extent of social network, and perceptions of loneliness and social isolation. Social isolation has been anecdotally reported in individuals suffering from various rare diseases (4, 5). Few studies have identified how social isolation affects people with rare diseases, despite the National Research Council's call for investigations into the linkages between social isolation and health (6). The impact of social isolation and social support has been explored in other populations. In their seminal work, House, Landis and Umberson (7) reviewed prospective epidemiological studies of social isolation in humans, and found that that social isolation was a significant risk factor for broad-based morbidity and mortality.

Operationally, social isolation is defined as the perception of a stigmatized environment, societal indifference, a personal-societal disconnection, or personal powerlessness (8). It is characterized by a lack of support system or a small/nonexistent social network. Few published studies have explored the experiences of living with a rare disease; no studies identified have investigated social isolation in rare lung diseases such as AATD or sarcoidosis.

Sarcoidosis is a rare, complex, granulomatous disease of unknown etiology. The incidence of sarcoidosis varies throughout the world, with 10-40 per 100,000 persons in the US and northern Europe developing this condition (9). Many organ systems can be affected, although lung involvement is most common, occurring in greater than 75% of all patients (10). Depression has been documented in these individuals (11), and more recently, social isolation has been identified as a concern (12). However, no published studies of social isolation have been identified to date.

Alpha-1 antitrypsin deficiency (AATD) is an uncommon genetic disease which that affects approximately 1 in 2,000 to 1 in 5,000 individuals and predisposes to liver disease and early-onset emphysema (13). Previous studies have confirmed adverse psychosocial effects related to an AATD diagnosis (14). Social isolation has been explored in individuals with COPD (15, 16) but no published studies were identified that investigated social isolation in AATD patients specifically.

Recognition of the importance of research into rare lung diseases is growing (17). Many studies have adopted a population-based approach to rare diseases, but the patients' viewpoint on having such a disorder has remained unattended (18). Despite the number of people affected by rare diseases, resources are lacking. Patients often feel isolated, unable to get the information and support they need (19). Delays in diagnosis and/or misdiagnosis may promote distrust of health care providers and counselors. Information on the psychosocial burden of these diseases is needed, of which social isolation is one component of the continuum.

Social isolation as a concept

The term "social isolation" has multiple meanings. Carpenito-Moyet succinctly defined social isolation as 'the state in which the individual or group expresses a need or desire for contact with others but is unable to make that contact' (20). Individuals at risk for such states include ethnic/cultural minorities, persons with chronic physiological and psychological illnesses or deformities, and elderly persons (8), such as individuals grappling with living with rare conditions.

In his concept analysis of social isolation in older adults, Nicholson (21) suggested that determinants of isolation include 'number of contacts, feelings of belonging, fulfilling relationships, engagement with others, and quality of network members' (p. 1349). Killeen suggests that isolation with choice is aloneness, while social isolation without choice equates to loneliness (22). This may be why some scales designed to measure loneliness also measure perceived social isolation or some measure of social network (e.g., the UCLA Loneliness Scale) (23).

This overview outlined the defining characteristics of social isolation and demonstrates that the term is not uniformly defined and consensus is elusive. This challenges measurement of the concept in this patient population. An integrative review of established instruments tested in diverse populations can inform studies that need to measure social isolation in populations living with rare disease such as sarcoidosis or alpha-1 antitrypsin deficiency.

For the purposes of this integrated review, instruments purporting to measure one or more constructs as delineated by Nicholson (21) (number of contacts, feelings of belonging, fulfilling relationships, engagement with others, and quality of network members) or Warren (stigmatized environment, societal indifference, personal-societal disconnection, or personal powerlessness) were included (8).

Objectives

The purpose of this paper is to present the findings of an integrative review of a number of instruments that were explicitly designed and tested to measure social isolation and concepts related to social isolation (such as loneliness or social support or network), and to review their relevance and appropriateness for the pilot measurement of social isolation in populations with sarcoidosis or alpha-1 antitrypsin deficiency.

Methods

The integrated review methodology publicized by Whittemore and Knafl (24) was utilized to examine studies related to the concept to fully comprehend the depth and breadth of information related to social isolation. This particular approach allows for the inclusion of diverse methodologies (i.e. experimental and non-experimental research) to provide for a more holistic assimilation of information.

Literature search

An extensive review of the literature was conducted using PubMed, Medline, CINAHL and PsycINFO databases encompassing a range of years, as indicated in the attached table, but in general, between 1970-2013. This range was chosen in order to capture any seminal works that may have been published. GoogleScholar was also utilized to refine reviews. The search terms entered were "sarcoidosis", "alpha-1" "social isolation", "social support", "instrument", "questionnaire", "loneliness", "chronic disease", "lung disease" "pulmonary disease, "respiratory disease" and "social support" and combinations of these terms. In addition, the following three questionnaires were also used in the initial search, under the assumption that these could lead to other instruments measuring the same or similar constructs: "Social Support Questionnaire (SSQ)", "Lubben Social Network Questionnaire", and "Friendship Scale". The initial search captured over 500,000 articles; after multiple refinements, a total of 11 studies were included which encompassed eight instruments (see figure 1).

Inclusion criteria

The inclusion criteria included published material with one of the search terms as the subject heading, and published in English. Literature relevant to instruments for measuring perceived social isolation or social support or loneliness was extracted from peer-reviewed journals. The initial search included the broader terms in order to assess for items within scales that might be similar to one another. Following this electronic search for articles, a hand-search of the references of the selected articles was conducted.

Exclusion criteria

Literature focusing on animal studies was excluded. Studies were excluded if they evaluated populations other than adults. Dissertation, theses, or websites were excluded.

Summary of the literature

As shown in Table 1, a total of 8 scales were reviewed from 11 studies. The theoretical frameworks ranged from Weiss' theory of social support used in the development of the Personal Resource Questionnaire-85 (PRQ85) (25) and Sarason's Social Support Questionnaire (26), the use of Kahn's social support theory in the development of the Norbeck Questionnaire (27) and various references to other social support theorists such as Cassel, Cobb and Bowlby in the Friendship Scale (28) and the Sarason Social Support Questionnaire.

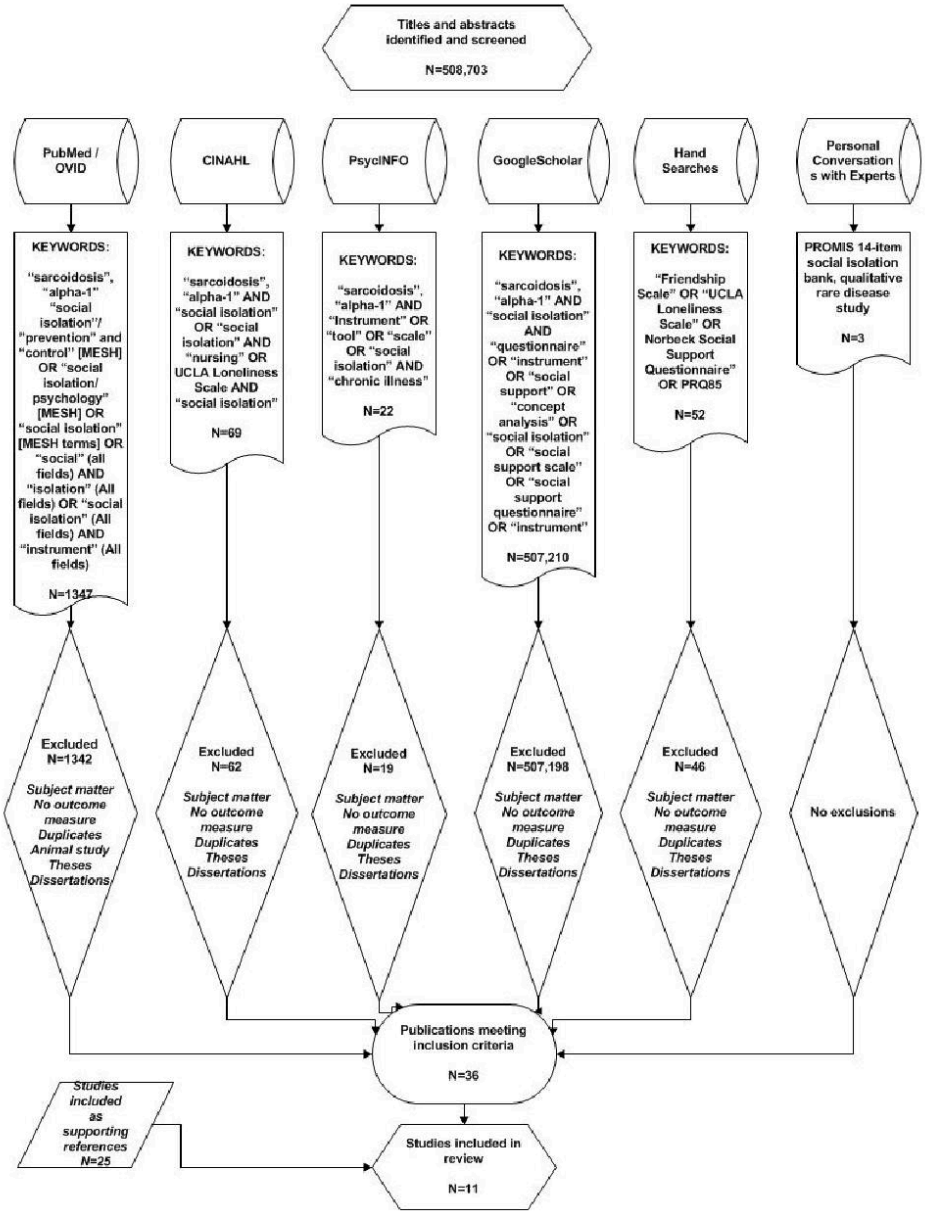

Figure 1. Search strategy.

Table 1.

Instrument/ Reference	Theoretical Framework	Sample/Subjects/ Disease/Condition	Instrument Description	Scoring	Method of Measurement	Reliability	Validity	Feasibility	Level of Evidence	Outcomes
Friendship Scale Hawthorne, G. (2006). Measuring Social Isolation in Older Adults: Development and Initial Validation of the Friendship Scale. *Social Indicators Research, 77*, 521-548.	Based upon three theories of social support (Cassel, Cobb, Bowlby)	(N=829). Four older adult cohorts, defined as those over 60 years, were recruited. Four cohorts were (1) older adults living in supported housing or nursing homes; (2) hospital outpatients with chronic disability; (3) older veterans; (4) healthy subjects from the community.	The six items measure six of the seven important dimensions that contribute to *social isolation* and its opposite, *social connection.*	Scoring involves reversal of items 1, 3 and 4 followed by summation across all items. The score range is 0–24. A high score represents social connectedness and a score of ''0'' complete social isolation.	Quantitative Questionnaire Self-administered	Cronbach α = 0.83	Correlates well with SF12 MCS, WHOQOL-Bref Psychological scale, AQoL Social relationships scale – Correlates *less well* with SF12 PCS, WHOQOL-Bref Physical scale, AQoL Physical senses scale	Short, 6 item questionnaire	1b	Initial paper outlining the development of the friendship scales .The psychometric properties suggest that it has excellent internal structures and that it possesses reliability and discrimination.
Functional Social Support Questionnaire Broadhead, W. E., Gehlbach, S. H., de Gruy, F. V., & Kaplan, B. H. (1988). The Duke-UNC Functional Social Support Questionnaire: Measurement of social support in family medicine patients. *Med Care, 26*(7), 709-723.	None specified	(N=401).Family medicine clinic patients selected from randomized time-frame sampling blocks during office hours. No specific disease or conditions noted.	8 item, 5 point Likert scale; contains questions in four content areas defined as *quantity of support, confident support, affective support and instrumental support*	The item response options are on a 5-point scale ranging from 1 (much less than I would like) to 5 (as much as I would like). Higher scores reflect higher perceived social support.	Interviewer or self-administered	Test-retest reliability evaluated over a 2-week time period. Correlation coefficient of .66. Item-remainder correlations were used to assess internal consistency and ranged from .50 for useful advice, to .85 for help around the house. To improve instrument reliability the original 14-item scale was reduced to eight items.	Construct validity demonstrated by significant correlations of individual items with measures of symptom status and emotional function. These measures have been shown to relate to social support. Concurrent validity was supported by significant correlations with 3 out of 4 activities measures.	Takes ~ 5 minutes to complete	1b	Reliability and validity for this scale was supported by the testing done as detailed in this study. The authors stated that the use of the scale in black, elderly, and male populations may be limited, and suggested further testing. They also suggested that the small number of items and the relative ease of completion should support its use as a cost-effective measurement tool.

Table 1. (Continued)

Instrument/ Reference	Theoretical Framework	Sample/Subjects/ Disease/ Condition	Instrument Description	Scoring	Method of Measurement	Reliability	Validity	Feasibility	Level of Evidence	Outcomes
Lubben Social Network Scale-6) Lubben, J. , Stuck, A. E. (2006). Performance of an Abbrev. Version of the Lubben Social Network Scale Among Three European Community-Dwelling Older Adult Populations. *The Gerontologist, 46*(4), 503-513.	None specified	(N= 7,432). Take from three populations Samples comprised of patients seen by family medicine clinic for a variety of conditions; no specific diseases or conditions noted.	6-item scale. It has been translated into many languages and applied to older adult populations of diverse ethnic backgrounds. Designed to gauge *social isolation* in older adults by measuring *perceived social support* received by family, friends and mutual supports (eg. neighbors), including confidant relationships. It consists of 6 items which measure size, closeness and frequency of contacts of a respondent's social network.	Score is an equally weighted sum of the 6 items. Scores range from 0 to 30 with higher scores indicating a greater level of social support and low risk for isolation. Scores for each question range from zero to five, with 0 = minimal social integration and 5= substantial social integration. A score < 20 may indicate a person with an extremely limited social network and high risk for isolation.	Quantitative Questionnaire Self-administered questionnaire with health professionals as informants	Internal consistency for the LSNS-6 was consistent across sites (a=0.83).	The validity for LSNS-6 was established using EFA and criterion validity	6 item scale. Also available in 18 and 12-item versions. Available for free via the developer's website.	1b	Across all samples, the LSNS-6 showed high internal consistency and a consistent factor structure, even though there were relevant differences among the three samples in terms of demographic and health characteristics
Norbeck Social Support Questionnaire Norbeck, J. S., Lindsey, A. M., & Carrieri, V. L. (1981). The development of an instrument to measure social support. *Nurs Res*, 30(5), 264-269.	Kahn's Social Support	(N=135). This initial testing of the NSSQ was done with 75 master's students in nursing and 60 senior nursing students. None of the subjects were presented as having a chronic disease or condition.	Total of 9 items. Participants list and rate the amount of Affect, Affirmation and Aid they perceive is available to them from up to 24 network members of their choosing. After completing the network list, they are instructed to successively turn the half pages and rate each listed network member (0–4) on six functional support questions measuring three types of support: affect, affirmation, and aid (see Table 1). Network members' support scores are then summed.	Because support ratings for each network member are summed, support scores (range = 0–576) vary greatly due to network size alone. Average scores have been suggested to eliminate the bias for subjects with multiple network members.	Quantitative Questionnaire Self-administered However, in part due to the 'free text' entry, Because of this self-report feature, the NSSQ requires a unique layout (available from Prof. Norbeck at no cost).	Pearson correlations among the items and subscales were calculated. • Each of the two items for each subscale, were highly correlated: Affect, .97; Affirmation, .96; and Aid, .89. • The correlations among the four items measuring Affect and Affirmation ranged from .95 to .98, suggesting that these two functions might not be distinct.	Affect, Affirmation, and Aid correlated with the C&L Emotional Support component at .51, .56, and .44, respectively. Affirmation correlated at .33 with the C&L Informational Support, but the correlation between Aid and the C&L Tangible	Free from author on UCSF College of Nursing Website Takes ~ 10 minutes to complete	1b	The Norbeck Social Support Questionnaire is a valid and reliable measure of total network support, as well as three functional types of social support. The three functional types of social support should be calculated

Instrument/ Reference	Theoretical Framework	Sample/Subjects/ Disease/ Condition	Instrument Description	Scoring	Method of Measurement	Reliability	Validity	Feasibility	Level of Evidence	Outcomes
						The correlations between the Aid items and the Affect and Affirmation items ranged from .72 to .78. • The correlations among the three network properties (Number in Network, Duration of Relationships, and Frequency of Contact) ranged from .88 to .96; and these network properties correlated highly with Affect and Affirmation (.88 to .97) and moderately with Aid (.69 to .80). Test-Retest Reliability. The test-retest correlations were Affect, .89; Affirmation, .88; and Aid, .86. Similar high correlations were found for the three network properties, which were each .92	Support was -.03; however, the C&L Tangible Support scale was a weak construct with a Coefficient Alpha of .31.			
Norbeck SSQ Gigliotti, E., & Samuels, W. E. (2011). Use of averaged Norbeck social support questionnaire scores. *ISRN Nurs*, 2011	Kahn's definition of social support	(N=609). A secondary analysis was conducted on data from three different samples of women who were mothers attending college for their first postsecondary school degree (n = 157, n = 263, n = 189). None of the subjects were presented as having a chronic disease or condition	Using a unique layout, participants are first asked to list from 1 to 24 network members "who provide personal support for you or who are important to you. After completing the network list, they are instructed to successively turn the half pages and rate each listed network member (0–4) on six functional support questions measuring three types of support: affect, affirmation, and aid. Network members' support scores are then summed.	Because support ratings for each network member are summed, support scores (range = 0–576) vary greatly due to network size alone.	Quantitative questionnaire Subject completed	Not purpose of this paper	Not purpose of this paper	Not purpose of this paper	2a	In all three samples, there are no statistically significant decreases in averaged total functional support scores, affect or affirmation as network size increases.

Table 1. (Continued)

Instrument/ Reference	Theoretical Framework	Sample/Subjects/ Disease/ Condition	Instrument Description	Scoring	Method of Measurement	Reliability	Validity	Feasibility	Level of Evidence	Outcomes
				In fact, in the three samples [9–11] used in the present study, network size was very highly correlated with affect scores (.95, .94, and .95, resp.) and affirmation scores (.92, .90, and .92, resp.) and a bit less with aid scores (.81, .82, and .82, resp.). As network size increased, support scores increased.						Thus, averaged total functional support scores and averaged affect and affirmation scores do not lower scores as one's network size increases. This is not true for averaged aid scores. In all three samples, there are stat. sig. decreases in averaged aid support scores as network size increases. Averaged Norbeck Social Support Questionnaire (NSSQ) support scores remove the influence of network size variability but may unduly lower scores for participants with large networks.
Norbeck SSQ Norbeck, J. S., Lindsey, A. M., & Carrieri, V. L. (1983). Further development of the Norbeck Social Support Questionnaire: normative data and validity testing. *Nurs Res, 32*(1), 4-9.	Kahn's social support	This was considered the second phase of testing the NSSQ. Involved three studies with sample sizes of 136, 75 and 55.	Participants are first asked to list from 1 to 24 network members "who provide personal support for you or who are important to you. After completing the network list, they are instructed to turn the half pages and rate each listed network member (0–4) on six functional support questions measuring three types of support: affect, affirmation, and aid. Network members' support scores are then summed.	Because support ratings for each network member are summed, support scores (range = 0–576) vary greatly due to network size alone.	Quantitative questionnaire Subject self-report		Construct validity of the instrument was established by comparing convergent and discriminant constructs to the NSSQ. Concurrent validity with another social support questionnaire was demonstrated. Predictive validity was tested in a sample of 53 graduate students through assessing the buffering effect of social support on measures of negative mood following life stress.		1b	In the second and third studies, the instrument was found to be very stable over a seven-month interval and sensitive to changes within the social support networks of a group of graduate students during their first year of study.

Instrument/ Reference	Theoretical Framework	Sample/Subjects/ Disease/ Condition	Instrument Description	Scoring	Method of Measurement	Reliability	Validity	Feasibility	Level of Evidence	Outcomes
PROMIS Item Bank Hahn, E. A., Devellis, R. F., Bode, R. K., Garcia, S. F., Castel, L. D., Eisen, S. V., . . . Group, P. C. (2010). Measuring social health in the patient-reported outcomes measurement information system (PROMIS): item bank development and testing. *Qual Life Res, 19*(7), 1035-1044.	None specified	(N=956) general population respondents who answered Ability to Participate and Satisfaction with Participation items.	These were items that were evaluated, and not a defined scale. The authors identified and reviewed 1,781 Social Function items; 112 items were retained and edited. New items were written to fill content gaps. This process produced 56 items for Ability to Participate and 56 for Satisfaction with Participation within four contexts (family, friends, work and leisure). All items were written as statements, using a 7-day reporting period.	The Ability items used a 5-point frequency rating scale (Never, Rarely, Sometimes, Often and Always) and the Satisfaction items used a 5-point intensity rating scale (Not at all, A little bit, Somewhat, Quite a bit and Very much).	Quantitative items	N/A	Content validity was sought by examining previous models and by collecting patient experiences about their social well-being and limitations [20, 21]. Sub-domain structures emerged from qualitative data, expert consensus and quantitative results of extensive field tests. Although Ability to Participate and its three subdomains were essentially unidimensional (based on EFA and CFA), they did not fit the item response theory model, when examined either separately or together	N/A	1b	After extensive item preparation and review, EFA-, CFA- and IRT-guided item banks help provide increased measurement precision and flexibility. Two Satisfaction short forms are available for use in research and clinical practice. This initial validation study resulted in revised item pools that are currently undergoing testing in new clinical samples and populations.
PRQ-85 Weinert, C. (1987). A social support measure: PRQ85. *Nurs Res, 36*(5), 273-277.	Weiss' model of relational functions	Three studies: sample of 132 older adults, 100 and 132 middle-aged adults. None of the samples were presented as having a chronic disease or condition.	Measures *situational and perceived social support*. Two part questionnaire: Part 1: 10 life situations where an individual might be expected to need assistance- provides information concerning the person's resources and satisfaction with the help received from those resources. Part 2: 25 item, 7-point Likert scale that measures the person's perceived level of social support	Scale scores range from 25-175; higher scores indicate higher levels of social support	Quantitative questionnaire Self-administered	Established in 3 separate samples of 132 and 100 subjects. Cronbach's alpha ranged from.87 (132 subjects) to .90 (100 subjects). Third sample (132 subjects) demonstrated alpha of .90.	Content validity was established by 2 nurse researchers not familiar with the instrument. Construct discriminate validity established using the BDI and Trait Anixety Scale. Moderate correlations were obtained between Part 2 of the tool and the BDI (r=.33) and the Trait Anxiety Scale (r=-.39).	Takes ~ 15 minutes to complete	1b	The findings from this initial use of the PRQ-85, combined with ~ 5 years of psychometrics on previous version of the tool (PRQ82) support validity and reliability of the instrument.

Table 1. (Continued)

Instrument/ Reference	Theoretical Framework	Sample/Subjects/ Disease/ Condition	Instrument Description	Scoring	Method of Measurement	Reliability	Validity	Feasibility	Level of Evidence	Outcomes
PRQ-85 Weinert, C., & Tilden, V. P. (1990). Measures of social support: assessment of validity. *Nurs Res, 39*(4), 212-216.	Weiss' model of relational functions	Two samples of adults N=333 who were part of a large health project and N=99 who participated in a methodological study.	The PRQ-85 Measures situational and perceived social support. Two part questionnaire: Part 1: 10 life situations where an individual might be expected to need assistance provides information concerning the person's resources and satisfaction with the help received from those resources. Part 2: 25 item, 7-point Likert scale that measures the person's perceived level of social support. The CRI is a self-report questionnaire which consists of 38 Likert type items purported to measure four subscales of social support: social support, reciprocity, cost and conflict	The PRQ-85 Scale scores range from 25-175; higher scores indicate higher levels of social support.	Quantitative questionnaire Self-administered	Internal consistency reliability was found to be .90 for the ORQ85 and for the CRI subscales: .93 for support, .95 for conflict, .81 for reciprocity and .92 for cost.	Convergence was evaluated and confirmed. Construct validity of the PRQ85 and CRI behave similarly. Discriminant validity was also assessed and found to be lacking across some of the subscales.	Both questionnaire are self-administered and take ~15 minutes to complete.	1b	Both of the instruments each measure social support. Each of the measures taps somewhat different aspects of social support and CRI scores may be more global and measure a larger and more tightly focused aspect of social networks.
Social Support Questionnaire (Sarason) Sarason, I. G., Levine, H. M., Basham, R. B., & Sarason, B. R. (1983). Assessing social support: The Social Support Questionnaire	Not based on one specific framework, although Weiss' theory of social support was cited, as well as Kelly and Caplan	Four studies included. Samples of college students: N=602, N=227, N=295 and N=40 in each study, respectively.	The SSQ is a 27-item scale which investigates (1) the *number of perceived social support events* in a person's life and (2) the degree to which they are personally satisfying.	Satisfaction rating for each situational circumstance is the same regardless of the situation given. A six point rating scale (from "very satisfied" to "very dissatisfied") is used to rate the individual's satisfaction with his or her support available. A support score for each item is calculated by the number of individuals the participant listed (number score)..	Quantitative Questionnaire Self-administered questionnaire	The number scores yielded an inter-item correlation ranging from 0.35 to 0.71 (m=0.54). The Cronbach's alpha for internal reliability was 0.97.	Criterion validity tests show a significant negative correlation between the SSQ and a depression scale (ranging from -0.22 to -0.43), and correlations of 0.57 and 0.34 were obtained between an optimism scale and the satisfaction score and the number score, respectively (Sarason et al., 1983).	5 minutes to administer	1b	The paper describes the development of the SSQ to measure social support. The reliability of the tool is quite high and correlates with other measures

Instrument/ Reference	Theoretical Framework	Sample/Subjects/ Disease/ Condition	Instrument Description	Scoring	Method of Measurement	Reliability	Validity	Feasibility	Level of Evidence	Outcomes
Journal of *Personality and Social Psychology, 44*(1), 127-139.				The overall support score (SSQN) is calculated by the mean of this scores across the items. The overall satisfaction score is calculated by the means of the 27 satisfaction scores (McDowell & Newell, 1996		The inter-item correlations for the satisfaction scores ranged from 0.21 to 0.74, and the coefficient alpha was 0.94. Test-retest correlations of 0.90 for overall number scores and satisfaction scores of 0.83 were obtained (Sarason et al., 1983).				The SSQ does not seem to be highly biased by the social desirability response set. The SSQ investigates two aspects of social support: (a) the number of perceived social supports in a person's life and (b) the degree to which they are personally satisfying.
UCLA Loneliness Scale (v3) Russell, D. W. (1996). UCLA Loneliness Scale (Version 3): Reliability, Validity, and Factor Structure. *Journal of Personality Assessment, 66*(1), 20.	Not stated	Data from four previous studies using the scale was used to assess the psychometrics of version three of the scale.Study 1 consisted of 489 college students; Study 2 consisted of 310 nurses; study 3 consisted of 316 teachers; 30 1 elderly comprised study 4	Developed to assess *subjective feelings of loneliness or social isolation.* It is a 20 item scale; 10 positively worded and 10 negatively worded items. The Scale has become the most widely used measure of loneliness, with over 500 citations in the Social Science Citation Index of the 1980 publication on the measure. Scores on the loneliness scale have been found to predict a wide variety of mental (i.e., depression) and physical (i.e., immunocompetence, nursing home admission, mortality) health outcomes in our research and the research of others	Choices range from 1 ("never") to 4 ("often"). Each person's responses to the questions are summed, with higher scores indicating greater loneliness.	Quantitative self-administered	Coefficient alpha ranges from .89-.94; test-test reliability over 1 year (r=0.73)	Convergent and construct validity supported by analyses of previous studies. CFA of multiple studies provided support for viewing the scale as a unidimensional measure.	Takes about 5 minutes to complete	1b	The data support the reliability and validity of the version 3 of the UCLA Loneliness Scale in a variety of populations, ranging from college students to the elderly. Psychometric data from version 3 are comparable to values reported for the first two versions.

Three of the instruments (the Functional Social Support Questionnaire, the Lubben Social Network Scale, the UCLA Loneliness Scale) as well as the PROMIS Social Isolation Item bank have unspecified theoretical foundations (29-31). The sample sizes for psychometric testing scores ranged from 55 subjects in the second phase of testing of the Norbeck Social Support Questionnaire (32) to 7,432 subjects for the Lubben Social Network Scale, distributed across three sites in Europe, with each site having greater than 1,900 participants at each (33).

None of the instruments reviewed were tested in rare disease populations. The Lubben Social Network Scale has been utilized in studies of patients with chronic obstructive pulmonary disease (34), a lung disease which can be caused, in rare instances, by alpha-1 antitrypsin deficiency. COPD and these rare lung diseases diseases share symptoms of breathing and mobility challenges, so that prior testing in those populations with strong psychometric performance helps support content validity in choosing to adapt them to study social isolation in sarcoidosis or alpha-1 antitrypsin deficiency patients.

Results

The search criteria included only studies of adults. In addition, the search was broadened to include studies of all disease populations, as no studies were identified that specifically explore social phenomena in sarcoidosis or alpha-1.

Evaluation of instruments

Seven instruments that assess adult perceptions of social support, measure social isolation or loneliness were identified: 1) the Friendship Scale, 2) the Lubben Social Network Scale, 3) the Norbeck Social Support Questionnaire, 4) the Personal Resource Questionnaire-85 [PRQ85], 5), the Social Support Questionnaire, 6) the UCLA Loneliness Scale – Revised and 7) the Functional Social Support Questionnaire, In addition, an eighth tool, an item bank derived from PROMIS [Patient-Reported Outcomes Measurement Information System] was included in this review. This 14 item bank of questions is referred to as the "Social Isolation Item Bank", and contains items purported to measure various facets of social isolation.

Instrument description

Instruments ranged from 6 items to 27 items comprising a scale. All instruments had the ability to be self-administered and all utilized at minimum, a Likert scale. The Friendship Scale, the PROMIS Social Isolation Item Bank, the UCLA Loneliness Scale and the Duke-UNC Functional Social Support Questionnaire gathered responses via only a Likert scale. The Lubben Social Network Scale is a composite instrument which utilizes a Likert scale as well as an ordinal ranking scale to confirm number of support persons available.

Two of the questionnaires required free text entry. Both the Sarason Social Support Questionnaire and the Norbeck Social Support Questionnaire asked the patient to list individual persons that they can count on for support. The Personal Resource Questionnaire-85 (PRQ-85) presented a listing of individuals (parent, spouse, friend, neighbor, etc) that the individual was asked to confirm as being available in times of help. The Duke-UNC Functional Social Support Questionnaire was reputed to be either self- or interviewer-administered. However, the instrument is presented to the patient as a Likert-scale, so it could easily be completed via patient self-administration.

Consistent with the lack of consensus definition of what constitutes social isolation is the variety of different constructs that the instruments measure. Although all of the constructs measured are linked to social isolation, the most common construct found in the review of instruments is perceived social support. The Personal Resource Questionnaire-85 (PRQ85), the Social Support Questionnaire and the Lubben Social Network Scale have all been found to measure this construct (25, 26, 33).

Method of perceptions and scoring

Four to 6 point Likert scales were most commonly used, with a summed lower Likert number generally indicating less social support (25, 29, 33, 35, 36) or

greater social isolation (31, 33, 37, 38). The (Sarason) Social Support Questionnaire provides two scores: an overall support score (SSQN) is calculated by the mean of scores across various situational circumstances. The overall satisfaction score is calculated by the means of the 27 satisfaction scores (26).

Method of administration

All instruments are completed via pencil and paper.

Reliability

In general, all of the studies spoke to reliability of the instrument on various levels. Of the eight instruments that were evaluated, all instruments with the exception of the Norbeck Social Support Questionnaire demonstrated acceptable internal consistency as supported by Cronbach's alpha scores >.70 (25, 26, 28, 29, 31, 33, 39). Since the Norbeck SSQ is not a summative scale, the reliability of this instrument was demonstrated using Pearson product-moment correlation calculations (27). Each of the two items for each subscale, were highly correlated: Affect, .97; Affirmation, 96; and Aid, .89. The correlations among the four items measuring Affect and Affirmation ranged from .95 to .98, suggesting that these two functions might not be distinct. The correlations between the Aid items and the Affect and Affirmation items ranged from .72 to .78. The correlations among the three network properties (Number in Network, Duration of Relationships, and Frequency of Contact) ranged from .88 to .96; and these network properties correlated highly with Affect and Affirmation (.88 to .97) and moderately with Aid (.69 to .80) (27).

Of the eight instruments evaluated, test-test reliability was reported for four of the instruments - the Duke UNC Functional Social Support Questionnaire, the Norbeck Social Support Questionnaire, the UCLA Loneliness Questionnaire, and the Sarason Social Support Questionnaire (26, 29, 31, 32) - and found to be acceptable (greater than .7). Four of the instruments - the PRQ85, the Friendship Scale, the Lubben Social Network Scale, and the PROMIS item bank - did not report this statistic (28, 33, 37, 39). The PROMIS item bank for social isolation is not a validated scale in and of itself. As such, reliability and validity estimates are not reported for this bank. Rather, researchers are free to access the various item banks from the PROMIS repository for use in testing.

Validity

Presentation of validity findings was inconsistent across the various studies. Concurrent validity was reported for three of the instruments, the Norbeck SSQ, the Friendship Scale and the Duke UNC Functional Social Support Questionnaire (27-29, 32). Convergent validity was noted for two of the eight tools, the UCLA Loneliness Scale and the Lubben Social Network Scale (31,33), and criterion validity was reported only for the Sarason SSQ (26).

Construct validity was noted for five of eight instruments, the Friendship Scale, the Lubben Social Network Scale, the UCLA Loneliness Scale, the Norbeck SSQ and and the Duke UNC Functional Social Support Questionnaire (28, 29, 31, 33, 35). These five instruments presented findings on factor analyses, demonstrating additional scientific rigor in validity testing. Factor analyses are used as an additional technique to assess the construct validity of an instrument, by statistically evaluating the internal structure of a scale and the various dimension(s) within that scale (40). Hawthorne performed a principal component analysis to evaluate construct validity for the Friendship Scale, and found that for six of the seven intended items, PCA results showed formed a unidimensional scale with mean loadings between 0.63 and 0.84 (28), and which is considered acceptable, since in general, a cut-off of .40 would be considered reasonable to retain the item (40). Lubben also reported on the factor analysis for the Social Network Scale, which incorporated an arbitrary cut-off of 0.5 (33). They found that the factor structure for the LSNS-6 was acceptable among the six items, and also reported eigenvalues of >1, suggesting a strong principle component. Broadhead performed factor analyses for the Duke UNC Functional Social Support Questionnaire which resulted in all of the items being retained, with r-values between .52 and .72 (29).

The validity of the PROMIS social isolation item bank was not reported.

Feasibility of instrument use

Feasibility is the ease and cost of instrument use, as well as time necessary for completion. Some questionnaires specifically requested that the user report back the results of any studies done using the instrument to the developer as per the developers' websites. The majority of the instruments require between 5 and 15 minutes to complete. It is not clear if all of the instruments are available in multiple languages, which is a desirable option.

Results

There are no validated instruments that measure social isolation (or social support, loneliness, or social networking) in these suffering from sarcoidosis or alpha-1 antitrypsin deficiency. No instruments were identified that measure any of these constructs in chronic interstitial lung disease.

In this particular review (as illustrated in table 1) a number of the studies reviewed did specify a theoretical framework that either guided the development of the instrument or the study overall. The findings of this review suggest that instruments proven to be valid and reliable in measuring social isolation do exist, albeit tested in other populations. The instruments reviewed have been tested in adult populations, in ages ranging from college-aged to older adults, and included a variety of races and ethnicities. This is encouraging when considering the instruments for use in the sarcoidosis or alpha-1 population and the fact that these patients are generally middle-aged to older adults. Somewhat discouraging is the fact that when demographics of the instruments were presented, the majority of the sample subjects were Caucasian. Of the eight instruments reviewed, five - the PRQ85, the Sarason Social Support Questionnaire, the Friendship Scale, the Lubben Social Network Scale and the UCLA Loneliness Scale- were lacking any information regarding race in the original psychometrics (23, 25, 26, 28, 33) and three - the Norbeck Social Support Questionnaire, the Duke-UNC Functional Social Support Questionnaire, and the PROMIS item bank - were evaluated in largely Caucasian populations (27, 29, 37). Thus, the utility of these instruments in culturally diverse and in rare disease populations warrants further exploration.

As shown in table 1, eight instruments were reviewed that measured social isolation, loneliness, social networking, social support or a combination thereof. It is important to note that some of the items overlapped between questionnaires. Of the eight instruments surveyed, two have published psychometric results that suggest potential generalizability in content validity, construct validity and cultural sensitivity: The Friendship Scale (28) and the UCLA Loneliness Scale (31). These two instruments contain items which closely link to the characteristics of social isolation as described by Nicholson (21) and Warren (8). The PROMIS Social Isolation item bank also could be considered for pretesting psychometric performance as a tool to assess social isolation. The tool has no psychometric testing results in any population to date but are available for consideration at: http://www.nihpromis.org. Pilot testing of the bank as a secondary measure would be appropriate in a one of these populations using another instrument as a primary assessment tool.

One of the major limitations of this review was the ability to conduct an equivalent comparison of the various tools. This was due in part to the inconsistency in the reporting of the psychometric properties of the tools, as well as the variety of different populations tested. As illustrated in the descriptions of the psychometrics of the instruments, in general, reliability and validity of these tools was acceptable in the populations studied.

Discussion

The experience of sarcoidosis or alpha-1 antitrypsin deficiency, as with other rare diseases, can be physically as well as emotionally devastating. In addition to the medical management of symptoms, there are numerous potential social consequences of living with a rare disease, including goal setting and life objectives. Equally as important, it may lead to

stigmatization, isolation and exclusion from one's social community. Sarcoidosis and/or alpha-1 may currently be considered "orphan" or rare diseases at the moment, but better, more refined medical diagnostics combined with tools to assist the clinician in screening for and managing psychosocial issues could provide for a more holistic overall approach to patient care.

The lack of a consensus definition of what constitutes social isolation, and how to measure it remains one of the main challenges for researchers interested in this phenomenon. Throughout the literature, the idea of perceived social support being an important component of the subjective perception of social isolation appeared frequently, and was in fact, the most common construct found in the review of instruments.

Conclusion

The experience of living with sarcoidosis or alpha-1 antitrypsin deficiency as with other rare diseases, has largely been understudied and poorly documented. Although the psychosocial issues associated with rare disease sufferers are many and varied, one common characteristic that many of these individuals share is the feeling of isolation. As a first step in exploring this phenomenon, the use of existing instruments would be of use in measuring the magnitude of social isolation in this population. The relatively small number of items on these questionnaires might lend themselves to web-based distribution (after consultation with the developers) for interested and consenting participants from a broad demographic area. Since populations in rare diseases are small and geographically dispersed, creative recruitment strategies would be beneficial, and consideration of web-based recruitment and/or test administration is warranted.

One construct not captured by any of the instruments identified in this search, or which was discovered in any literature search, is perceptions of public support for the care or cure of the disease. Public empathy for rare disease support is an important component of the reported experience of many rare diseases. Exploration among rare disease populations, by qualitative methods such as cognitive interviewing and focus groups, to learn whether these perceptions are a quantifiable construct in social isolation will inform content and construct validation of social isolation instrumentation in the study of persons with rare diseases.

Relevance to clinical practice

As the era of genomics and genetics continues to evolve and expand, it is likely that conditions that were unrecognized previously may be identified as disease conditions. Moreover, simplification and enhancement of testing for rare and/or genetic conditions is becoming more commonplace, and more clinicians may be faced with managing such patients. Knowledge of the potential or actual social impact of such conditions is necessary in order to provide for holistic management of such patients, and simple, existing tools can be useful. This review provides for a summary review of tools available to clinicians to screen for perceived social isolation in rare lung disease patients, a valuable asset to any clinician.

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1.3. Perceptions of Social Isolation and Social Support in Individuals with Alpha-1 Antitrypsin Deficiency and Sarcoidosis: A Mixed-Methods Study

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Abstract

Objective: This parallel, convergent mixed-methods study aimed to explore the perceptions of social isolation and social support in individuals living with alpha-1 antitrypsin deficiency or sarcoidosis.

Methods: 244 participants completed a series of online questionnaires, including the Friendship Scale and the Medical Outcomes Study – SocialSupport Survey (MOS-SSS). 29 individuals participated in qualitative interviews. Logistic regression was conducted to explore whether any of the clinical or demographic characteristics were predictive of higher/lower social isolation or social support scores. Qualitative content analysis was conducted to identify themes. Results of the analyses of the two data sets were triangulated to provide a rich portrait of social isolation and social support as experienced by these individuals.

Results: There were significant differences in the Friendship Scale, MOS-SSS emotional support, positive social interaction and total scores between the alpha-1 and sarcoidosis groups, with higher scores observed in those with alpha-1 (indicating more social connectedness and perceived support). Sarcoidosis- affected individuals who participated in support groups reported more social isolation as reflected in the ranks for Friendship Scale scores than those who did not participate in support groups (p=0.04). Content analysis revealed six themes: Self-reflection, building connections, activities, knowledge, relationships and physical/psychological impact. Triangulation revealed that scores on both instrument measures were supported by the qualitative data in both groups.

Conclusion: Less perceived social isolation and more perceived social support were reported in the alpha-1 population compared with the sarcoidosis population. Social isolation can be measured and serves as a target for interventions in rare disease populations.

Introduction

In recent years, focus on rare diseases has been increasing. An estimated 30 million Americans live with a diagnosis of one of the 6,000 to 8,000 known rare diseases [1] and such conditions affect approximately 30 million individuals in the European Union [2]. Two of these conditions – sarcoidosis and alpha-1 antitrypsin deficiency (AATD) – most often affect the lungs, although other organ involvement occurs.

Sarcoidosis is a chronic, progressive, multisystem granulomatous disease of unknown etiology [3] for which there is no known cure. The clinical presentation of sarcoidosis varies and is dependent upon organ and system involvement. Some individuals present with no physical symptoms, while others may have severe breathlessness (those with pulmonary involvement), tumor-like growths on the skin or face (skin sarcoidosis or lupus pernio), or uveitis (ocular involvement). The incidence and prevalence of sarcoidosis varies worldwide, although regional variations exist. In the U.S., sarcoidosis is more common in African Americans, with incidence rates as high as 40 per 100 000/year, compared to Whites with an incidence rates range of 5–11 per 100 000/year [4].

AATD is a rare inherited disorder that causes lung and liver disease due to mutations in the gene SERPINA1, which codes for alpha-1 antitrypsin (AAT). The clinical presentation of AATD can vary, and is dependent upon a variety of factors, including genotype. The genetic deficiency predisposes individuals to early-onset emphysema, one of the phenotypes of COPD [5], although chronic bronchitis and asthma can also occur. AATD is a metabolic-genetic disease that, in its classical and most typical form, is caused by homozygosity for the AAT mutant Z gene. These protease

inhibitor (PI) “Pi*ZZ” genotypes, occur in 1 in 2000 to 3500 births in North American and European populations [6]. In the United States, prevalence estimates suggest that there are between 70,000–100,000 AAT-deficient individuals, although only 10% have been identified [7].

Rare diseases are often chronic, complex and associated with physical, intellectual or neurological disabilities that may inhibit participation in life activities, thus creating risk for isolation [8]. Yet, few published studies have explored the experiences of living with a rare disease. Studies investigating the perspective of individuals living with scleroderma identified persistent themes of stigma and isolation [9], although this disease is characterized by skin disease obvious to others. Henderson et al. [10] investigated the general psychosocial impact of living with Niemann Pick disease Type B, a rare lysosomal storage disorder, and observed that those patients reported feelings of social isolation. A survey of over 200 general practitioners (GP) in Ireland revealed that 28% perceived that rare disorders can result in feelings of isolation [11]. Whether diseases that have no obvious outward signs impact feelings of isolation remains unstudied.

Social isolation is defined as "a state in which the individual lacks a sense of belonging socially, lacks engagement with others, has a minimal number of social contacts and where the individual is deficient in fulfilling and quality relationships" [12]. Over the past three decades, studies have shown social isolation to be predictive of mortality and morbidity in the general population [13, 14, 15] and in populations with chronic conditions [16, 17]. Despite the high number of individuals affected by rare diseases as a whole, patients with rare disease often report feeling isolated and unable to

get the information and support needed [18]. To date, no studies have specifically explored social isolation in rare lung diseases such as AATD or sarcoidosis.

Although recognition of the importance of research into rare lung diseases has been growing [19], this focus has been primarily from the biomedical perspective, with less attention given to the psychosocial aspects. To address this gap in rare disease research, the overall objective of our study was to gain insight into perceptions and consequences of social isolation and social support as experienced by individuals with AATD and sarcoidosis. In addition, we sought to gain preliminary understanding of the effects of participation in support groups in these individuals. The overarching question driving this mixed methods study was: *How do individuals with the rare lung diseases of AATD and sarcoidosis perceive and describe the social impact and consequences of living with these diseases?*

Methods

Design

We applied a parallel convergent mixed-methods design to explore perceptions of the social impact of living with one of two rare diseases. This design facilitated the collection and analysis of two independent data streams, one quantitative and one qualitative, simultaneously with subsequent comparison and merging of findings to develop a more complete understanding of the social impact of rare lung disease [20].

Participants

Our goal was to recruit an equal distribution of AATD and sarcoidosis participants. Individuals with AATD were recruited through the Alpha-1 Foundation Research Registry using an email sent by the registry coordinator. Sarcoidosis

participants were recruited through snowball sampling beginning with individual participants of a sarcoidosis support group familiar to the PI. To be eligible, individuals were required to be adults who self-reported a physician diagnosis of AATD or sarcoidosis with pulmonary involvement, and confirmed their ability to read and speak English. There was no specific timeframe required for diagnosis. Individuals were required to have access to a computer with a valid email address (for purposes of completing instruments via the Research Electronic Data Capture REDCap survey site).

Data Collection

Participants completed online surveys of validated measures of social isolation and social support through using (REDCap), an electronic web-based data collection system [21]. We randomly selected a subgroup of participants who consented to take part in subsequent qualitative interviews to obtain rich data on perceptions of social support and relationships with others. A qualitative descriptive approach guided the interviews to gain a description of social isolation and associated consequences in everyday terms from the participants [22].

Measures

Demographics and Clinical Characteristics. We collected general demographic information as well as years since diagnosis, disease condition (sarcoidosis or AATD), genotype (AATD), disease severity (sarcoidosis), presence of pain or fatigue, frequency of leaving the home within the prior week, participation in support or advocacy groups and participation in outside activities.

Pulmonary status. Due to the pulmonary involvement associated with these diseases, we sought to quantify the effects of breathlessness on everyday activities. The modified

Medical Research Council (mMRC) Dyspnea Score was used to assess the severity of perceived breathlessness on a five-point scale (0-4) [23].

Social Isolation. The Friendship Scale [24] is a six-item Guttman scale that measures perceived social isolation. The scale assesses both critical aspects of social isolation: perceived social isolation (3 items) and perceived emotional loneliness (3 items). Scores for each item range from zero to 4 with a total score ranging from zero to 24. Cutpoints to classify levels of social isolation range from 0-11 (very socially isolated) to 22-24 (very or highly socially connected) [24]. The psychometric properties of the scale in the validation study conducted in older adult populations in various types of settings suggest excellent internal structures as assessed by structural equation modeling (CFI = 0.99, RMSEA = 0.02), reliability (Cronbach's alpha = 0.83), and discrimination when assessed against two other short social relationship scales [24, 25, 26]. A subsequent validation study in individuals with low back pain showed similar results [25]. Tests of concurrent discriminant validity suggest it is sensitive to the known correlates of social isolation [24].

Social Support. We evaluated perceived social support using the Medical Outcomes Study: Social Support Survey (MOS-SSS). The scale is a 19-item instrument containing four domains to assess perceived availability of social support, including (1) emotional/ informational support, (2) tangible support, (3) positive social interaction and (4) affectionate support [27]. Responses are scored via a 5-point Likert-type scale, and range from "none of the time" to "all of the time". Scores range from 0-100 with higher scores indicating more perceived support. Sound psychometrics of the MOS-SSS were established in the original validation study by Sherbourne and Stewart [27], with

Cronbach's alpha ranging from 0.91 to 0.97 for the various subscales and high convergent and discriminant validity of items. Subsequent and supportive validation studies were also conducted with Chinese [28], Portuguese [29] and Black individuals [30].

Qualitative Interviews

Interviews took place via telephone. An interview script comprised of eight questions was used to facilitate approximately 60-90 minutes of dialogue, although modified where appropriate.

- I'd like to start by having you describe a typical day
- Can you tell me a little bit about how having <<alpha-1/sarcoidosis>> has affected your life? What place does it have in your life?
- How have people in your life reacted to your having <<alpha-1/sarcoidosis>>?
- Can you tell me a little bit about how having <<alpha-1/sarcoidosis>> has affected your relationships with other people?
- Can you tell me what happens if you ask others for help?
- Tell me a bit how you access support for your condition
- What do you do for enjoyment?
- Can you tell me a little bit about why you chose to participate in this study?

Semi-structured questions and prompts were used to yield narratives centering on social isolation and/or social support. All interviews were audio recorded and transcribed.

Statistical and qualitative analysis

During the quantitative data analysis, data were exported from the REDCap database to SPSS v22 [31] for analysis. The primary analysis used all available data from all subjects who attempted completion of the questionnaires. Any respondents missing an item were excluded only from tests involving that item.

Descriptive statistics were computed on the demographic and clinical characteristics of the study population. For categorical and ordinal variables frequencies were calculated and reported. For continuous variables, measures of central tendency

including mean, median and standard deviation were calculated. All continuous variables were assessed for normality and all distributions of variables were skewed except age; therefore, appropriate non-parametric analysis methods were used. For age, the two groups were compared using the independent samples t-test; other continuous variables were compared using the Mann-Whitney U-test.

Mean total scores (with 95% CIs) and median scores were calculated for the pooled study population and individual disease groups, for both the Friendship Scale and MOS-SSS. The average Friendship Scale and MOS-SSS scores are broken down by condition in the table below and the ranks compared using the Mann-Whitney-U test (Wilcoxon rank-sum test). To assess the effect of support group participation, the pooled study population was dichotomized into individuals who reported participating in online or face-to-face support groups and those who reported not participating in such groups. Non-parametric Mann-Whitney test was utilized to compare the two groups.

Logistic regression was conducted to explore whether any of the demographic or clinical characteristics might be predictive of higher/lower social isolation or social support scores. The Friendship scale was dichotomized into those who were very isolated, isolated, and with some isolation [range of scores 0-18] versus the socially connected and very socially connected (range of scores 19-24)[25]. The MOS-SSS was dichotomized to indicate those who perceived low-normal social support (below 75th percentile; scores ≤ 85.5) or high social support (above or equal to the 75th percentile; scores >85.5) [32]. Predictor variables were entered individually, and the individual effects on the dependent variable(s) of isolation or social support were compared.

Qualitative analyses of interview data were conducted using NVivo10 qualitative software [33] and directed content analysis [34, 22]. Each interview was transcribed after the completion of the interview and the transcript was reviewed in conjunction with the audio recording. The investigator read the transcripts and used an initial coding approach to abstract passages in an exploratory manner. Interview transcripts were coded line-by-line and themes and subthemes developed [35]. After initial themes were identified, additional data abstraction occurred, including compression of themes [36] and review by an expert qualitative nurse scientist for confirmation of themes.

Quantitative and qualitative findings were merged to create a robust preliminary profile of individuals' perceptions of social isolation and social support. After merging the two data streams, divergence, convergence and other relationships were explored [20].

Ethics approval

Institutional Review Board (IRB) approval was obtained at the Medical University of South Carolina. The study was approved for a waiver of signed consent and participants were provided with a Statement of Research upon accessing the online survey. All data were cleaned of any potentially identifying information to maintain participant anonymity and confidentiality.

Results

Sample

A total of 244 participants completed the online questionnaire, 177 with AATD and 67 with sarcoidosis. For the sarcoidosis population, 75 participants were contacted and enrolled via snowball sampling; 67 completed the questionnaires. For the AATD

population, a total of 1125 potential participants were contacted in two separate email "blasts" by the Alpha-1 Registry coordinator, (562 participants in the first email, followed by 563 different participants in the second email). Of those, 177 subjects completed the online questionnaires. The initial goal of an equitable distribution of AATD and sarcoidosis participants was not achieved due to the limited access to and response of sarcoidosis patients in comparison with the AATD group, and was likely skewed due to the access facilitated by the AATD registry coordinator.

For the qualitative phase of the study, subjects responded to a single question at the end of the online questionnaire indicating their willingness to participate in an interview. Eighty four percent (205/244) of the subjects who participated in the questionnaire completion agreed to participate in the interviews; of those, twenty-nine (15=AATD, 14=sarcoidosis) were randomly selected to complete semi-structured, individual interviews.

AATD subjects were statistically significantly older (59.4 (SD=11.4) than sarcoidosis participants (50.1 (SD=8.3), $p<0.0001$). There were was a significant difference in the gender make-up of the two populations: there was a larger proportion of males in the AATD group (37.4%) than in the sarcoidosis group (16.4%), while there was a smaller proportion of females in the AATD (62.6%) group compared to the sarcoidosis group (83.6%) (p=0.002).

Overall, the study population was primarily female (n=165, 68.5% of all participants). Pi*ZZ was the most common genotype for alpha-1 participants (97; 55.7%), followed by MZ (32; 18.4%). Most sarcoidosis participants did not know the stage of their disease (39; 60.0%) although 18 subjects confirmed that they had either the more severe Stage 3

or 4 disease (9, 13.8% for each stage). The majority of subjects in both populations were married. More subjects in the alpha-1 population (93; 53.4%) lived with a spouse or partner than in the sarcoidosis population (24; 35.8, %, p=0.003). The vast majority was white and less than 6% of the population self-reported as Hispanic. Annual household income ranged from $25,000 to $99,000. Additional details are reported in **Table 1**. More alpha-1 individuals participated in face-to-face support groups (26.3% vs. 13.6%, p=0.04), while more sarcoidosis patients participated in online support groups (87.9% vs. 28.0%, p<0.001).

Table 1 Demographic and clinical characteristics overall and by disease

Variable	Study population n=244	Alpha-1 n=177	Sarcoidosis n=67	*p*-value
Age, mean (SD)	56.6 (11.4)	59.4 (11.4)	50.1 (8.3)	*<0.001
Gender				
Male	76(31.5)	65(37.4)	11(16.4)	*0.002
Female	165(68.5)	109(62.6)	56(83.6)	
Marital status, n(%)				
Married	154(64.7)	113(65.7)	41(62.1)	0.31
Single	17(7.1)	12(7.0)	5(7.6)	
Divorced	43(18.1)	27(15.7)	16(24.2)	
Widowed	7(2.9)	7(4.1)	0	
Partnered	17(7.1)	13(7.6)	4(6.1)	
Living situation				
Alone	39(16.2)	32(18.4)	7(10.4)	*0.003
With spouse/life partner	117(48.5)	93(53.4)	24(35.8)	
With children	16(6.6)	7(4.0)	9(13.4)	
With spouse/life partner & children	54(22.4)	33(19.0)	21(31.3)	
With a friend	5(2.1)	2(1.1)	3(4.5)	
Other	10(4.1)	7(4.0)	3(4.5)	
Race				
White	226(93.0)	173(98.3)	53(79.1)	<0.001
Black or African American	11(4.5)	1(0.6)	10(14.9)	
American Indian or Alaska Native	1(0.4)	0	1(1.5)	
Asian Indian	1(0.4)	0	1(1.5)	
Other	4(1.6)	1(0.6)	3(4.5)	
Annual household income (per year)				
<$10,000	15(6.8)	10(6.1)	5(8.6)	0.82
$10,000-$24,999	34(15.4)	24(14.7)	10(17.2)	
$25,000-$49,999	58(26.2)	42(25.8)	16(27.6)	
$50,000-$99,999	81(36.7)	63(38.7)	18(31.0)	
$100,000+	33(14.9)	24(14.7)	9(15.5)	
MRC Dyspnea Score, n (%)				
0	27(11.3)	19(10.9)	8(12.3)	0.63
1	82(34.2)	64(36.6)	18(27.7)	
2	97(40.4)	66(37.7)	31(47.7)	
3	26(10.8)	20(11.4)	6(9.2)	
4	8(3.3)	6(3.4)	2(3.1)	
Participates in face to face support groups, n (%)	55(22.8)	46(26.3)	9(13.6)	*0.04
Participates in online support groups, n (%)	107(44.4)	49(28.0)	58(87.9)	*<0.001
Participates in advocacy groups	56(23.2)	41(23.3)	15(23.1)	0.97

**Statistically significant at the 0.05 level*

Social isolation and social support scores

There were statistically significant differences in the Friendship Scale, MOS-SSS emotional support positive social interaction domains and MOS-SSS total scores between the two groups, with higher scores observed in those with alpha-1 (indicating more social connectedness and perceived support). Although not statistically significant, the other domain scores of the MOS-SSS (tangible support and affectionate support) were also slightly higher in the AATD group. A comprehensive overview of scores is provided in **Table 2**.

Table 2: Average Friendship Scale and Medical Outcomes Scale – Social Support Survey (MOS-SSS) by Study Population and Condition

	All, (n=244)		Alpha-1, (n=177)		Sarcoidosis, (n=67)		W	Z	p-value
	Mean *(95% CI)*	**Median *(IQR)***	**Mean *(95% CI))***	**Median *(IQR)***	**Mean *(95% CI)***	**Median *(IQR)***			
Friendship Scale	16.3 (15.5-17.1)	17 (12-22)	17.0 (16.1-17.9)	18 (13-22)	14.5 (12.9-16.1)	15 (9-20)	6682.5	-2.595	*0.009
MOS-SSS emotional/ informational support	27.3 (26.1-28.4)	29 (21-34)	28.1 (26.8-29.4)	30 (21-35.5)	25.0 (22.9-27.1)	24 (20-32)	6761.5	-2.427	*0.015
MOS-SSS tangible support	14.2 (13.5-14.8)	16 (10-20)	14.5 (13.7-15.3)	16 (10-20)	13.3 (11.9-14.6)	14 (8-18.3)	7089.5	-1.821	0.07
MOS-SSS positive social interaction	11.2 (10.7-11.6)	12 (8-15)	11.5 (11.0-12.0)	12 (9-15)	10.3 (9.3-11.3)	12 (6.5-15)	6740.0	-2.096	*0.04
MOS-SSS affectionate support	11.6 (11.1-12.1)	13 (9-15)	11.8 (11.2-12.4)	13.5 (9-15)	10.9 (9.9-12.0)	12 (7-15)	6916.5	-1.504	0.13
MOS-SSS Transformed total	63.8 (60.3-67.3)	68.4 (42.1-85.5)	66.4 (62.4-70.5)	73.7 (47.4-88.2)	56.9 (50.0-63.7)	62.5 (35.2-75.0)	5975.0	-2.481	*0.01

**Statistically significant at the 0.05 level*

Support Group participation

As illustrated in **Table 3**, no differences in ranks were observed for either instrument scores for the overall population in terms of who had participated in support groups compared to those who had not participated in support groups. This applied to the AATD population as well. However, in the sarcoidosis population support group

participants had lower Friendship Scale scores (and thus, were more isolated) compared to those who did not participate in support groups (with higher scores indicating more isolation).

Table 3: Friendship Scale and Medical Outcomes Scale – Social Support Survey (MOS-SSS) by Study Population and Condition by Access to Support

	Accessed support		Did not access support		W	Z	p-value
	Mean *(95% CI)*	Median *(IQR)*	Mean*(95% CI))*	Median *(IQR)*			
All respondents							
Total, N	**134**		**108**				
Friendship Scale	15.9 (14.8-17.0)	17 (11-21.5)	16.9 (15.7-18.0)	18 (13-22)	15256.5	-1.211	0.22
MOS-SSS Transformed total	63.0 (58.3-67.6)	68.4 (41.8-83.2)	64.9 (59.4-70.4)	69. (43.4-90.8)	13930.5	-0.635	0.53
Alpha-1							
Total, N	**75**		**100**				
Friendship Scale	17.4 (16.1-18.7)	19 (13-22)	16.7 (15.5-17.9)	17 (13-21.5)	8153.5	-0.734	0.46
MOS-SSS Transformed total	68.7 (62.8-74.5)	75 (52.6-88.6)	64.7 (59.0-70.5)	66.4 (43.1-90.1)	7319.0	-0.754	0.45
Sarcoidosis							
Total, N	**59**		**8**				
Friendship Scale	13.9 (12.2-15.6)	14.4 (9-20)	18.9 (13.7-24.1)	22.5 (13.8-23)	1836.5	-2.096	*0.04
MOS-SSS Transformed total	55.6 (48.3-62.86)	57.9 (34.2-75.0)	67.1 (38.7-94.5)	73.7 (43.4-96.1)	1679.5	-1.18	0.24

** Statistically significant at the 0.05 level*

Predictors of isolation and support

As illustrated in Table 4 and Table 5 in the Appendix, and using the isolation cut points described previously, females had twice the odds of males to report perceptions of social isolation (OR=2.10; *p*=0.01, 95%CI [1.21, 3.66]), and single and divorced persons had almost 4 times the odds of married individuals to report isolation (OR=3.66 and 3.72; *p*=0.03 and 0.001, 95% CI [1.14, 11.74] and [1.71, 8.08] ,respectively). Individuals who lived alone were also twice as likely to report feeling isolated (OR=2.30; *p*=0.03, 95% CI [1.09, 4.88]). Those with more severe breathlessness, as indicated by the MRC Dyspnea scale score of 3 or 4 (OR=3.58; *p*=0.03, 95% CI [1.17, 11.01]), or those with more severe sarcoidosis staging of Stage 3 or 4 (OR=7.78; *p*=0.03, 95% CI [1.17, 51.92]) were also

more likely to report feelings of isolation. Individuals with visual impairments had higher odds of reporting isolation than those who did not have such sight impairments (OR=2.99; p=0.04, 95% CI [1.06, 8.38]). Odds of reporting significant isolation were higher for persons who reported difficulties with activities of daily living such as concentrating (OR=7.28; p<0.001, 95% CI [3.57, 14.86]), walking up stairs (OR=3.38; p<0.001, 95% CI[1.97, 5.83]), dressing/bathing (OR=2.73, p<0.001, 95% CI[1.48, 5.01]) or doing errands (OR=3.65; p<0.001, 95% CI [2.04, 6.52]) compared to their counterparts. Odds of reporting significant isolation were also higher for individuals who reported pain within the prior 30 days (OR=1.07; p<0.001, 95% CI [1.04-1.10]) or fatigue within the prior 30 days (OR=1.06; p<0.001, 95% CI [1.04, 1.09]) compared to their counterparts.

The risk factors for lower social support presented in Table 6 and Table 7 included female sex (OR=2.09; p=0.02, 95%CI [0.94, 1.00]), and living alone (OR=4.51; p=0.02, 95%CI[1.33, 15.34]). Also, the odds of low social support increased for single (OR=3.28; p=0.13, 95%CI [0.72, 15.05]), divorced (5.78, p=0.01, 95% CI [1.69, 19.75]), and widowed participants (OR=2.81; p =0.35, 95%CI [0.33, 24.06]) compared to married participants. Medical factors associated with lower social support included an MRC dyspnea scale ≥3 or 4 (OR=3.97; p=0.12, 95%CI [0.69, 22.82]), difficulty concentrating (OR=2.75; p =0.01, 95% CI [1.26, 6.02]), any pain within the prior 30 days (OR=1.04; p =0.01, 95% CI [1.07, 10.7]) or fatigue within the prior 30 days (OR=1.06: p<0.001, 95% CI [1.03, 1.09]).

Qualitative description of social impact of Rare Disease

After initial coding and compression of codes from the qualitative interviews, six main themes related to the social impact of the disease emerged: *Self-reflection, building connections, activities, knowledge, relationships, and physical/psychological impact.*

Self-reflection

The concept of self-reflection emerged as participants described becoming more insightful and thoughtful about the effect of having a rare disease on their lives. Six individuals (20.7%) described engaging in activities that facilitated self-reflection to help them cope, whether by meditation or verbalizing some form of gratitude as a result of their condition.

Building connections

All of the participants (n = 29, 100%) described "building connections" with others. These connections were grouped into subcategories of *altruism*, *volunteering*, and a *support network*. Often, the introduction to a support network was due to the participant's desire for additional information after initial diagnosis, and led to the individual feeling a connection to the group. Such connections were often formed as a result of feelings of isolation.

> *...support is very important; you do feel very isolated with this disease…..There is not a lot of medical information out there. We certainly kick each other's brains a lot; what you want, what you being treated with, how much of it they using, how you feel, how do you feel afterwards….*

We're all in this together. No matter what we do, when we do it or how we do it we can make a contribution, all it takes is little time, effort and caring and baby steps…we're making strides and something that we'd only discovered 50 years ago, which is incredible. When you look at other conditions, I think the Alpha-1 community is so progressive in its thinking and in how it generates information and enthusiasm to help the little ones that are struggling with this and maybe we'll see a cure in their lifetime.

Individuals spoke of their experiences volunteering, participating in various support group venues, and a sense of altruism as a result of their condition. Six individuals reported volunteering, and most of these activities were not related to their disease. Activities included church events, free clinic work and education. Twenty-eight individuals (96.6%) spoke of their experiences with a support network, (family, friends, organizations like the Alpha-1 network, or Facebook sites and groups). Some individuals felt that the online sites were negative, with individuals using the sites to vent complaints. A sarcoidosis participant reported:

I am in a Facebook group and I told my son I find when I am reading some of their posts I get really frustrated because they will be asking.. well, have you ever had this or what do you suggest to take if you have low potassium… It's really a strange thing because it's constant complaining.

Participants with sarcoidosis also often spoke of face-to-face meetings being widely geographically dispersed, difficult to attend, and poorly attended. As one individual stated:

I tried to occasionally attend a sarcoid support group in Portland but that is 140 miles one way. It's hard to drive that far. I do belong to Inspire Online (an online support group community). I post there occasionally. I read there. I have a group that I met from there. One of them I met face to face. We have a group of seven of us and we have a little private Facebook group.

Activities

Participants described the impact of rare disease on their ability to engage in routine activities of daily living, including outside activities as well as household responsibilities and socialization with others. Twenty-two individuals (75.9%) verbalized impact of the disease on their activities and/or lifestyle, oftentimes leading to feelings of isolation due to their inability to actively socialize. Individuals described an intuitive sense of how to pace themselves, however:

I do have to pace myself, I get very tired. And I never feel good, I never ever feel good.

Relationships

Nineteen (73.1%) of the participants discussed their experiences with seeking help, which was often a change in established roles with family or friends. That it, many moved from the "giver" role to the "recipient" role, in terms of assistance. In general, many individuals were reluctant to ask for help early in the disease process. As one participant shared:

I hate asking for help, I really do…My husband is a great help and my kids have stepped up more and helped and they're of an age now where they can. 13 and 16

is definitely old enough to help, but I don't want to be that person that asks for help because of any issue.

Descriptions of relationships with children varied, with some individuals sharing about the positive relationships that they had with their children, despite the disease, while others voiced concern about the effect that the disease had on their children:

It is really hard for her. She remembers mom being able to do more with other kids. There is a seven or eight years difference between her and my oldest. She remembers me being much more active; much more able to go do things.

Married participants spoke abundantly about the role of spousal support:

He and I have researched and done everything we can and we still will do everything that we can to try to get help for this disease and that's one thing I'm very fortunate that I have someone that cares that much and loves to be that involved with me with it.

Physical/psychological impact

The impact on physical or mental well-being was coded under the umbrella of physical or psychological impact. In general, reports of physical impact were from those with sarcoidosis and specific to fatigue or pain. In terms of psychological impact, acceptance was a strong and recurring theme among many individuals. Participants frequently reported fear at time of diagnosis.

Individuals spoke of becoming isolated as a result of the disease. Whether they drew back or others pulled away from them, it was clear that this was a major impact of the disease:

I have a couple of them still call; I have some that talk to me on Facebook but for the most part my friends have gone because I don't have the common things that we used to working together. So, I don't have the friendships that I used to have…. but for the most part I feel pretty lonely

For some, the isolation was so pronounced that it threatened their very existence:

Mostly there are days that are so lonely and so – just – that I have actually said to my physician I promise you I cannot live the rest of my life this way and I meant every ounce of the word.

Merging of Data through Triangulation

This mixed methods study was designed to elicit an understanding of the depth and breadth of perceptions of social isolation and social support in populations with sarcoidosis or alpha-1. To achieve this, the two data streams were merged via data triangulation. The essence of a triangulation approach is the ability to utilize two methods to conduct independent assessments of the same phenomena [37] and to then integrate the findings. The integration in this study consisted of combining the narrative qualitative data with the numeric quantitative data. Although these two sets of analyses were conducted independently, the intent was that the qualitative data would provide depth and breadth of understanding to the findings from the quantitative data (Figure 1). This parallel mixed analysis resulted in a convergence (and in some cases, divergence) of findings that would not be apparent with a single approach. The figure below illustrates the process by which this parallel mixed analysis was carried out:

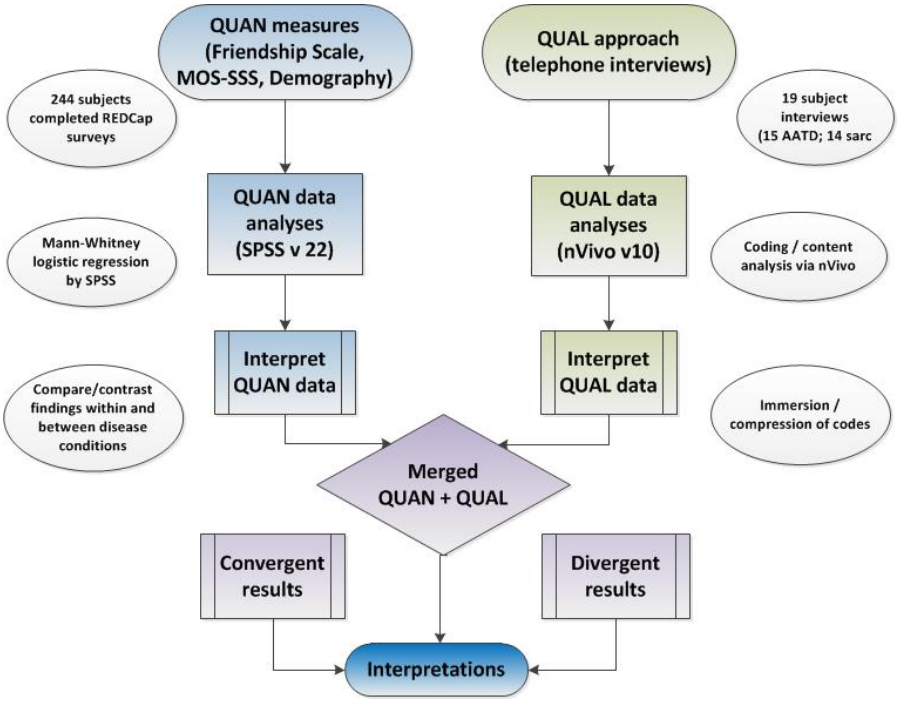

Figure 1: Process of parallel mixed analysis

Although there was much discussion regarding the physical aspects of the disease, triangulation focused on exploring the narrative comments and their confirmation with or contradiction to each subgroup's mean scores of the Friendship Scale and the MOS-SSS. Common themes mentioned by multiple participants are listed in the qualitative portion of the summary table (Table 8). Merged findings are presented with quantitative scores of the two instruments first, followed by qualitative findings that confirm or contradict the quantitative scores [20]. This data merging process produced a comprehensive, albeit somewhat limited (due to the size and nature of the study) understanding of this population's perceptions of social isolation and social support.

Results of the triangulation analysis indicated that in general, sarcoidosis participants perceived lower social support, even though they participated in various online communities. Alpha-1 patients had higher social support scores, and spoke more

frequently of family support. Both groups described feeling isolated, and these feelings were reflected in the quantitative Friendship Scale scores. The sarcoidosis group – which was more overt in their description of feeling isolated, also had lower Friendship Scale scores as compared to the alpha-1 group; those differences were statistically significant. For those participants whose direct quotes are featured in Table 3, individual scores are provided. In general, when comparing individual scores on the two instruments with what participants stated qualitatively, there was good alignment, with the exception of few outlying instances

Discussion

Unlike previous studies of populations with rare diseases, this study explored similarities and differences between two groups with rare lung diseases. It demonstrates successful conduct of a study in rare groups using virtual methods, which can be a viable option for groups that are geographically dispersed, or for the ultra-rare diseases. Using a mixed methods approach, the study design facilitated the analysis of a large number of perspectives on the social impact of their disease, both quantitatively as well as allowing for a more in-depth understanding of these concerns and responses via qualitative interviews. Due to the robust response of the AATD community in particular, a large number of participants were enrolled, increasing the power of the study to detect differences.

Findings that individuals who suffer from rare diseases may experience feelings of social isolation and perceive a lack of social support are not unexpected. What may not be apparent using one form of data collection and analysis is that these phenomena are often multi-layered, and that often, the disease's effect on functional capacity can

spur the vicious cycle of isolation. Although individuals reported feeling supported, it is also evident that some of that support came from virtual communities (such as Facebook) with their inherent assets and shortcomings. One obvious asset is accessibility irrespective of geography. An individual can "speak" to a community without having to overcome transportation and distance challenges, which can be a hurdle in those with physical or financial constraints. One liability that has not been discussed at length in the literature is that in some virtual communities, there may be an underlying sense of "complaining" or "disease one-upmanship", as some individuals use the virtual boards to voice a litany of complaints or compare illness notes. The most important finding in this study was the fact that despite the seemingly "ease of access" of virtual communities, a number of individuals felt that the tone of many of the groups was negative, and so they sought to break off and start their own closed groups.

There were subtle differences between the populations that became apparent during data analysis. For example, although many of the AATD participants knew their genotype, the majority of sarcoidosis participants did not know their stage of lung involvement. This may be due to the fact that in this population, staging is not discussed as frequently as organ involvement when individuals self-classify. There were more AATD participants who reported being active in face-to-face support groups than sarcoidosis participants, and conversely, more sarcoidosis participants who reported activity in online support groups than AATD individuals. This may be driven in part by the paucity of live support groups available to sarcoidosis patients, and also due to the influence and reach of the groups sponsored by the Alpha-1 Foundation.

The AATD population in this study scored higher on both instruments, indicating more perceived social support and less isolation. These participants frequently mentioned the presence and impact of the Alpha-1 Foundation and its organized communities, whereas there was no mention of sarcoidosis organizational involvement in this sample of sarcoidosis patients. In addition, as there are approved therapies for alpha-1 (Alpha-1 Protease Inhibitor, A1PI), individuals who are managed with this therapy also are assigned to an Alpha-Net coordinator (who also has the condition) who facilitates care, and often acts as a de facto support person. Among participants, these coordinators often took the place of support group(s), and were spoken of very highly during the interviews. In general, there were few divergent findings. Both groups reported some measure of social support, and some social isolation; much of the qualitative data were convergent with the instrument scores.

The implications of these findings suggest that support groups and support persons can be effective in enhancing the lives of individuals with rare diseases. Future research should examine the similarities and differences of both live and virtual support groups, and explore structured and unstructured formats for both populations. A more structured, facilitated sarcoidosis support group could provide additional data to inform tailoring of future support groups for both populations and recommendations for facilitating support groups.

Limitations

There were a number of limitations inherent in the study. All participants were recruited virtually; the results may not be representative of individuals who tend to be more mobile, or participate in live support groups. Although the study was conducted

virtually, the two populations were accessed using different approaches. The AATD participants were part of the MUSC Alpha-1 registry, and by nature, had already consented to the idea of participating in research. There was likely some degree of relationship with the coordinator and/or investigator and so there may have been some bias in terms of their willingness to participate in this study. The sarcoidosis participants were contacted via convenience or snowball sampling, and were generally not part of an established unit, such as the MUSC Alpha-1 Registry. However, by virtue of knowing an individual who was sharing information about the study, some measure of community bias could have been present. All participants were located in the U.S., and per the study protocol, were required to have computer access in order to complete the survey; this may limit the generalizability of the findings. Limitations related to lack of computer access cannot be dismissed, and the effects of the digital divide still exist. Kontos and colleagues [38] found that in the U.S, lower socioeconomic status, older, and male adults were less likely to engage in a number of eHealth activities compared to their counterparts. In the U.S., sarcoidosis disproportionately affects African-Americans [39], who often face other economic challenges. Challenges with enrollment were also noted in a recent web-based survey of sarcoidosis patients including limited access to the internet, failure to complete surveys, disengagement from healthcare providers and concerns about protection of personal information [40].

Although no participants voiced concerns about the instruments chosen to measure social isolation or social support, and there was very little missing data, the method of dichotomizing the scales to measure isolation and social support may have diluted some of the information about the magnitude of isolation in the populations.

However, as this was a pilot study and we sought to mirror previous approaches using categorical variables, we chose to follow precedent, rather than revert to using continuous measures.

Conclusion

This population of individuals with AATD or sarcoidosis reported significant disease-related concerns, and the majority utilized some form of support group or person. Often, support-seeking was prompted by the individual seeking information. The use of virtual communities was a common theme, although many of these communities were criticized by the very individuals they sought to serve because of the tone of negativity that occasionally, permeated the discussion threads. It may be that such communities would benefit from the oversight of a facilitator not unlike the established Alpha-Net coordinator, although issues and challenges of trust also accompany that potential solution. The ability to measure patient concerns quantitatively, along with enhancing that information with subjective comments garnered through interviews may help in crafting future interventions to facilitate support in these populations, as well as other rare groups. Future research should further examine the phenomena of social isolation and social support in larger studies and also include other hypothesized predictors of these feelings.

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Appendices

(Intended for use as online supplementary material)

As illustrated in **Table 4**, females had twice the odds of males to report perceptions of social isolation (OR=2.10; p=0.01, 95%CI [1.21, 3.66]), and single and divorced persons had almost 4 times (OR=3.66 and 3.72; p=0.03 and 0.001, 95% CI [1.14, 11.74] and [1.71, 8.08] ,respectively) the odds of married individuals to report isolation (OR=3.66 and 3.72; p=0.03 and 0.001, 95% CI [1.14, 11.74] and [1.71, 8.08] ,respectively). Individuals who lived alone were also twice as likely to report feeling isolated (OR=2.30; p=0.03, 95% CI [1.09, 4.88]).

Table 4: Associations between Demographic Characteristics and Perceived Isolation

	Isolated, n(%)	OR	95% CI	Wald	df	p-value
Age		0.96	0.94-0.99	8.37	1	*0.004
Gender						
Male**	33(43.4)	1		6.92	1	*0.01
Female	100(61.7)	2.10	1.21-3.66			
Marital Status						
Married**	71(47.0)	1		14.66	4	*0.01
Single	13(76.5)	3.66	1.14-11.74			*0.03
Divorced	33(76.7)	3.72	1.71-8.08			*0.001
Widowed	3(42.9)	0.85	0.18-3.91			0.83
Partnered	9(52.9)	1.27	0.46-3.46			0.64
Living situation						
Not alone**	105(52.5)	1		4.75	1	*0.03
Alone	28(71.8)	2.30	1.09-4.88			
Annual household income (per year)						
<$10,000**	11(78.6)	1		19.25	4	*0.001
$10,000-$24,999	27(79.4)	1.05	0.23-4.83			0.95
$25,000-$49,999	38(65.5)	0.52	0.13-2.07			0.35
$50,000-$99,999	34(42.5)	0.20	0.05-0.78			*0.02
$100,000+	14(43.8)	0.21	0.05-0.91			*0.04
Ethnicity						
Hispanic, Latino/a or Spanish origin**	7(53.8)	1		0.01	1	0.72
Not of Hispanic, Latino/a or Spanish origin	124(55.4)	1.06	0.35-3.26			
Race						
White**	123(55.2)	1				
Non-white	9(60.0)	1.22	0.42-3.542	0.13	1	0.65

**significant at the 0.05 level; ** reference category*

As illustrated in **Table 5**, individuals who self-reported more severe breathlessness, as indicated by the MRC Dyspnea scale score of 3 or 4 (OR=3.58; p=0.03, 95% CI [1.17, 11.01]), or those with more severe sarcoidosis staging of Stage 3 or 4 (OR=7.78; p=0.03, 95% CI [1.17, 51.92]) were also more likely to report feelings of isolation.

Individuals with visual impairments (OR=2.99; p=0.04, 95% CI [1.06, 8.38]) had higher odds of reporting isolation than those who did not have such sight impairments (OR=2.99; p=0.04, 95% CI [1.06, 8.38]). Odds of reporting significant isolation were higher for persons who reported difficulties with activities of daily living such as concentrating (OR=7.28; p<0.001, 95% CI [3.57, 14.86]), walking up stairs (OR=3.38; p<0.001, 95% CI[1.97, 5.83]), dressing/bathing (OR=2.73, p<0.001, 95% CI[1.48, 5.01]) or doing errands (OR=3.65; p<0.001, 95% CI [2.04, 6.52]) also had higher odds of reporting significant isolation compared to their counterparts. Odds of reporting significant isolation were also higher for individuals who reported pain within the prior 30 days (OR=1.07; p<0.001, 95% CI [1.04-1.10]) or fatigue within the prior 30 days (OR=1.06; p<0.001, 95% CI [1.04, 1.09]) had higher odds of reporting significant isolation compared to their counterparts.

Table 5: Associations between Clinical Characteristics and Perceived Isolation

	Isolated, n(%)	OR	95% CI	Wald	df	p-value
Condition						
Alpha-1**	90(52.0)	1		3.30	1	0.07
Sarcoidosis	43(65.2)	1.72	0.96-3.10			
Genotype						
ZZ**	49(51.6)	1		2.03	3	0.57
SZ	9(50.0)	0.94	0.34-2.57			0.90
MZ	19(59.4)	1.37	0.61-3.09			0.45
MS/SS/Other	6(37.5)	0.56	0.19-1.67			0.30
Severity						
Stage 1 or 2**	3(37.5)	1		4.49	1	*0.03
Stage 3 or 4	14(82.4)	7.78	1.17-51.92			
MRC Dyspnea Score						
0**	14(51.9)	1		11.16	3	*0.01
1	34(44.4)	0.74	0.31-1.78			0.50
2	54(57.4)	1.25	0.53-2.96			0.61
3 or 4	27(79.4)	3.58	1.17-11.01			*0.03
Blind or serious difficulty seeing						
No**	115(53.2)	1		4.31	1	*0.04
Yes	17(77.3)	2.99	1.06-8.38			
Difficulty concentrating, remembering or making decisions,						
No**	70(42.4)	1		29.7	1	*<0.001
Yes	59(84.3)	7.28	3.57-14.86			
Difficulty walking or climbing stairs						
No**	35(37.6)	1		19.33	1	*<0.001
Yes	98(67.1)	3.38	1.97-5.83			
Difficulty dressing or bathing						
No**	83(49.1)	1		10.45	1	*0.001
Yes	50(72.5)	2.73	1.48-5.01			
Difficulty doing errands alone						
No**	68(44.7)	1		19.17	1	*<0.001
Yes	65(75.7)	3.65	2.04-6.52			
Number days (in past 30) pain made usual activities hard		1.07	1.04-1.10	23.6	1	*<0.001
Number days (in past 30) fatigue made usual activities hard		1.06	1.04-1.09	27.12	1	*<0.001
Number days (in past 7) left house or apartment		0.92	0.87-0.96	12.03	1	*0.001
Participates in online support groups						
No**	71(54.2)	1		0.27	1	0.61
Yes	61(57.5)	1.15	0.68-1.92			
Participates in face to face support groups						
No**	107(58.8)	1		3.01	1	0.08
Yes	25(45.5)	0.58	0.32-1.07			
Participates in advocacy groups						
No**	103(56.9)	1		0.82	1	0.36
Yes	28(50.0)	0.757	0.42-1.38			
Participates in Groups/activities participated in outside the home						
No**	55(76.4)	1		16.88	1	*<0.001
Yes	78(46.7)	0.271	0.15-0.51			

**significant at the 0.05 level; ** reference category*

As illustrated in **Table 6**, females again had twice the odds of reporting low-normal social support (OR=2.09; p=0.02, 95%CI [0.94, 1.00]). Those who lived alone had over four times the odds of reporting low to normal social support (OR=4.51; p=0.02, 95%CI[1.33, 15.34]). Also, the odds of low social support increased for being single (OR=3.28; p=0.13, 95%CI [0.72, 15.05]), being divorced (5.78, p=0.01, 95% CI [1.69, 19.75]), and being widowed participants (OR=2.81; p =0.35, 95%CI [0.33, 24.06]) increased the odds of low social support compared to married participants.

Table 6: Associations between Demographic Characteristics and Social Support

	Low-normal social support n(%)	OR	95% CI	Wald	df	p-value
Age		0.97	0.94-1.00	4.78	1	*0.03
Gender						
Male**	46(65.7)	1		5.15	1	*0.02
Female	120(80.0)	2.09	1.11-3.94			
Marital Status						
Married**	96(68.1)	1		10.30	4	*0.04
Single	14(87.5)	3.28	0.72-15.05			0.13
Divorced	37(92.5)	5.78	1.69-19.75			*0.01
Widowed	6(85.7)	2.81	0.33-24.06			0.35
Partnered	9 (69.2%)	1.06	0.31-3.61			0.93
Living situation						
Not alone**	133(71.5)	1		5.84	1	*0.02
Alone	34(91.9)	4.51	1.33-15.34			
Annual household income (per year)						
<$10,000**	10(83.3)	1		10.45	4	*0.03
$10,000-$24,999	28(90.3)	1.87	0.27-12.85			0.53
$25,000-$49,999	46(85.2)	1.15	0.21-6.23			0.87
$50,000-$99,999	49(66.2)	0.39	0.08-1.93			0.25
$100,000+	22(68.8)	0.44	0.08-2.39			0.34
Ethnicity						
Hispanic, Latino/a or Spanish origin**	7(63.6)	1		0.73	1	0.39
Not of Hispanic, Latino/a or Spanish origin	158(75.2)	1.74	0.49-6.17			
Race						
White**	155(74.9)	1		0.02	1	0.89
Non-white	11(73.3)	1.12	0.33-3.55			

**significant at the 0.05 level; ** reference category*

As illustrated in **Table 7**, an MRC Dyspnea score of ≥3 or 4 was associated with lower social support (OR=3.97; p=0.12, 95%CI [0.69, 22.82]). Those individuals who reported difficulty concentrating (OR=2.75; p =0.01, 95% CI [1.26, 6.02]), any pain within the prior 30 days (OR=1.04; p =0.01, 95% CI [1.07, 10.7]) or fatigue within the prior 30 days (OR=1.06: p<0.001, 95% CI [1.03, 1.09]) also had higher odds of low social support.

Table 7: Associations between Clinical Characteristics and Social Support

	Low-normal social support n(%)	OR	95% CI	Wald	df	p-value
Condition						
Alpha-1**	116(72.0)	1		2.44	1	0.12
Sarcoidosis	51(82.3)	1.80	0.86-3.76			
Genotype						
ZZ**	65(74.7)	1		2.51	3	0.47
SZ	12(80.0)	1.35	0.35-5.25			0.66
MZ	19(61.3)	0.54	0.23-1.28			0.16
MS/SS/Other	10(71.4)	0.85	0.24-2.97			0.79
Severity						
Stage 1 or 2**	5(71.4)	1		0.35	1	0.55
Stage 3 or 4	14(82.4)	1.87	0.24-1465			
MRC Dyspnea Score						
0**	17(77.3)	1		5.35	3	0.15
1	53(69.7)	0.678	0.22-2.06			0.49
2	68(73.9)	0.833	0.28-2.50			0.75
3 or 4	27(93.1)	3.97	0.69-22.82			0.12
Family history of condition						
No**	63(76.8)	1		1.24	1	0.27
Yes	68(69.4)	0.68	0.35-1.34			
Deaf or serious hearing difficulty						
No**	154(74.8)	1		0.33	1	0.56
Yes	13(81.3)	1.46	0.40-5.34			
Blind or serious difficulty seeing						
No**	150(73.9)	1		1.84	1	0.18
Yes	16(88.9)	2.28	0.63-12.71			
Difficulty concentrating, remembering or making decisions						
No**	106(69.7)	1		6.40	1	*0.01
Yes	57(86.4)	2.75	1.26-6.02			
Difficulty walking or climbing stairs						
No**	60(70.6)	1		1.58	1	0.21
Yes	107(78.1)	1.49	0.80-2.76			
Difficulty dressing or bathing						
No**	112(72.7)	1		2.19	1	0.14
Yes	55(82.1)	1.72	0.84-3.53			
Difficulty doing errands alone						
No**	101(70.6)	1		4.44	1	*0.04
Yes	66(83.5)	2.11	1.05-4.23			
Number days (in past 30) pain made usual activities hard		1.04	1.01-1.07	6.02	1	*0.01
Number days (in past 30) fatigue made usual activities hard		1.06	1.03-1.09	13.84	1	*<0.001
Number days (in past 7) left house or apartment		0.96	0.91-1.01	2.10	1	0.15
Participates in online support groups						
No**	85(70.2)	1		3.20	1	0.07
Yes	80(80.8)	1.78	0.95-3.36			
Participates in face to face support groups						
No**	128(76.2)	1		0.54	1	0.46
Yes	37(71.2)	0.77	0.38-1.55			
Participates in advocacy groups						
No**	126(74.6)	1		0.08	1	0.78
Yes	39(76.5)	1.11	0.53-2.31			
Participates in Groups/activities participated in outside the home						
No**	60(88.2)	1		8.57	1	*0.003
Yes	107(69.0)	0.297	0.13-0.67			

**significant at the 0.05 level; ** reference category*

As illustrated in **Table 8,** and in general, sarcoidosis patients perceived lower social support, although this group tended to report participating in online communities. Few of the sarcoidosis subjects interviewed spoke of participating in live support groups, and for those that did, the groups were small and sparsely attended. Both groups utilized Facebook groups, although the usefulness of these groups appeared to be in question. The AATD participants spoke more often of family support, while the sarcoidosis participants spoke more of peer support.

SUMMARY OF MANUSCRIPTS

Overview of Manuscripts' Contribution to the Question of Perceived Social Isolation and Social Support in Individuals with Alpha-1 Antitrypsin Deficiency or Sarcoidosis

Results of a dimensional concept analysis of social isolation served as a springboard for the work leading to the dissertation study. Findings from this analysis revealed that the central theme of having limited or low engagement in social networks is the defining characteristic of individuals experiencing perceived social isolation. Often, this phenomenon occurs over time in individuals who live with a chronic illness. Individuals who exist in a stigmatized environment – perceived or actual – are at risk for social isolation (Chambers et al., 2015; Warren, 1993). These individuals may benefit from such interventions as peer-based counseling, live support groups or internet-based support, and further study of these strategies is warranted. A salient finding from the concept analysis was that social isolation remains widely defined, and a consensus definition has not yet been reached. In the rare disease community, having cogent definitions of the various components of social isolation is critical in order to explore the phenomena, as having a rare disease can be an isolating experience (Patsos, 2001). Of the published studies reviewed to support the dimensional analysis, no studies were conducted in rare disease groups. Following that concept analysis, an integrative review of existing instruments designed to measure perceived social isolation was conducted, using concepts aligned with the aspects of social isolation identified in the dimensional analysis to guide instrument identification. From that review of eight instruments, two

were identified as suitable candidates to be used in pilot study in rare disease patients. Ultimately, the six-item Friendship Scale was chosen as the instrument for the dissertation study.

Since no published studies were identified that explored either perceived social isolation or social support in AATD or sarcoidosis patients, a convergent parallel mixed methods design was chosen to address this gap. This approach facilitated quantitative measurement of the concepts, and also applied a patient-centric approach, whereby the narratives from qualitative interviews, conducted in a random subset of subjects, were compared with the perceived social isolation scores and social support scores on the instruments.

The product of the dissertation was a robust overview and profile of patient perceptions of social isolation and social support that incorporates both quantitative scores as well as qualitative perspectives. One finding of note was that despite the frequent use of the Internet and associated chat rooms, Facebook groups and other social media, many individuals were dissatisfied with the tone of these groups, and so sought to remove themselves from larger groups. Occasionally, this was done in numbers, such that a breakaway subgroup of special interest patients was then formed, often as a private group. This finding of the use of the Internet for support is supported by the literature (Patsos, 2001; Schumacher et al., 2014), but the concerns over the negative tones contributes to the existing knowledge.

Subtle differences between the two populations became apparent during the data analyses. In this study population, many of the AATD participants knew their genotype, but the majority of sarcoidosis participants did not know their stage of lung involvement.

In future studies, it may be prudent to determine the type of caregiver(s) that manage these patients, and the length of time that participants have been under the current provider's care. This could shed some light on the patient-clinician relationship, the ability of individuals to access specialist clinicians, as well as to the level of knowledge that the participant possesses. This information would be helpful in order to inform future interventions. There were more AATD participants who reported being active in face-to-face support groups than sarcoidosis participants, and conversely, a larger proportion of sarcoidosis participants who reported activity in online support groups than AATD individuals. This may be driven in part by the paucity of live support groups available to sarcoidosis patients, and also due to the influence and reach of the groups sponsored by the Alpha-1 Foundation.

The AATD population in this study scored higher on both instruments, indicating more perceived social support and less isolation than the sarcoidosis participants, although the AATD population still scored "somewhat isolated". Both groups scored as perceiving low to normal social support, with the sarcoidosis participants reporting lower social support than their AATD counterparts. The AATD group frequently mentioned the presence and impact of the Alpha-1 Foundation and its organized communities, and in fact, this group as a whole reported more frequent participation in face to face support groups than the sarcoidosis participants. Of note is the fact that by nature, social isolation is likely to be difficult to alleviate in traditional one-on-one interventions, as this phenomenon may be more embedded in varying levels of interpersonal interaction than other social phenomena or social challenges (Cruwys et al., 2014). For example, although individual counseling may work, it may be more helpful to address it in both individual

interventions as well as group settings. One working hypothesis is that due to the "forced" social interaction afforded by these live groups, individuals obtained more benefit than those who engaged (usually alone) via their computer, but this study was not designed to test this hypothesis. Future studies could be designed to assess the magnitude of involvement with a participant's respective support group or system, in order to tease out further insights.

Various predictors of perceived social isolation and social support were identified in the study. Single and divorced persons and those that lived alone had higher odds of reporting social isolation, as did females. Those with impaired functional capacity, as measured by perceived breathlessness, or more severe sarcoidosis (as measured by staging), were more likely to report feeling isolated. Individuals who reported challenges with certain activities of daily living such as concentrating, walking up stairs , dressing/bathing, doing errands or who reported pain, fatigue or visual impairments also had higher odds of reporting significant isolation compared to their counterparts reporting less impairment.

Similar results were noted when exploring predictors of low social support. Females were twice as likely as their male counterparts to report feelings of low social support. Individuals who were single, divorced or widowed or lived alone also had higher odds of reporting low social support than those who were married or lived with someone. Individuals who experienced high levels of dyspnea had more than twice the odds of reporting low social support. Individuals who reported difficulty concentrating, pain, or fatigue had higher odds of reporting perceptions of lower support than their counterparts.

Limitations of Dissertation Research

Limitations of the research are provided within each manuscript. For the concept analysis of social isolation, there was little published literature identified regarding the phenomenon in individuals with chronic lung disease. There were also challenges with searching for literature on the phenomenon: since the concept remains somewhat open to interpretation, the term "loneliness" is often used interchangeably with "social isolation". The same limitation was found when searching the literature for the integrative review of instruments. In addition, the psychometrics of the instruments were reported inconsistently, and this proved to make for a challenge in ensuring equitable comparisons. In terms of the dissertation study, the populations of interest were accessed in two different ways. The alpha-1 participants were already part of an existing registry, and so there may have been some bias in terms of their willingness to participate in this study. The sarcoidosis participants were generally contacted via convenience or snowball sampling, and were typically not part of an established unit, such as the MUSC Alpha-1 Registry. Limitations related to lack of computer access cannot be dismissed, and have been noted in other studies of sarcoidosis patients. In the U.S., sarcoidosis disproportionately affects African-Americans(Rybicki, Major, Popovich, Maliarik, & Iannuzzi, 1997), who often face other economic challenges. Specific challenges relating to the recruiting of these individuals were underscored by Dr. Alicia Gerke in regard to her survey of sarcoidosis patients (Crouser & Judson, 2015). Limited access to the internet, failure to complete the surveys, disengagement from healthcare providers and a related lack of trust, such as concerns about protection of their personal information, were identified as common deterrents(Crouser & Judson, 2015). All participants were located

in the U.S., and per the study protocol, were required to have computer access in order to complete the survey; this may limit the generalizability of the findings.

Lessons Learned

The relative ease of recruiting the proposed sample – both in terms of recruitment time and numbers –was not anticipated. The role of the existing MUSC Alpha-1 registry coordinator, who had already established a relationship with the Alpha-1 population, even if only via email, cannot be understated. This registry coordinator was invaluable in the initial engagement of the potential study participants from this population. The investigator had an established relationship with a number of active sarcoidosis patients who reached out to their own networks, and this snowball sampling approach also benefitted the study enrollment. The investigator was transparent in disclosing that she was not diagnosed with either condition, and that this work was to support a doctoral study and pursuit of an academic credential. This transparency seemed to facilitate open dialogue between subject and investigator.

Further characterization of the population in terms of functional capacity would have been helpful in order to consider physical limitations that could affect individuals' mobility and ability to move about within their communities. The investigator collected information about genotype (in the case of the Alpha-1 population) or staging (in the case of the sarcoidosis population), as well as breathlessness via subject self-report on a dyspnea scale. Future studies would be well-served to collect additional information such as oxygen use, concomitant medications, and perhaps other comorbidities.

Importance of theory, model or framework to guide overall findings

Social network theory suggests that there is a positive effect of social networks and social support on an individual's coping resources, as well as the community resources that they are able to access(Heaney & Israel, 2008). Heaney suggested that social networks and social ties can enhance an individual's overall health status, facilitate the gathering of information, and ultimately, contribute to an individual's ability to problem-solve (Heaney and Israel, 2008). This illustration of the relationship between social networks and social support, and an individual's overall health status was the overarching hypothesis referenced for the design of this study - *individuals who accessed support would be less likely to perceive isolation or low social support, irrespective of the type of support that they accessed*. An individual's social network, consisting of both individual and community resources, was also hypothesized to be linked to the robustness of one's connectedness and feelings of support. Our findings are somewhat contradictory to the model, and suggest that for some individuals (such as the sarcoidosis population in our study), accessing support is not necessarily associated with less social isolation and higher social support scores. These findings, however, should be interpreted with caution, as more information would be needed (such as comorbidities, concomitant medications, etc) in order to draw causal inferences.

Research Trajectory

Further research in this area is warranted. This dissertation was designed as an exploratory study and was conducted with a small sample that was limited to a population the investigator could access with relative ease. Larger studies are needed that explore more geographically diverse populations, with a broader range of demographics. Future

studies should also enroll participants from a variety of settings, including live or ground-based clinics and/or support groups, in order to compare similarities and differences. Future studies should also include measures to further characterize the population, such as including oxygen and concomitant medication use. An ideal approach would be to convene a group of stakeholders and harness the power of a community-based participatory research approach, in order to design studies that not only answer the research question(s) of interest to the investigator, but also to explore issues that are important to patients. Findings from such studies could then be used to design interventional studies of various modalities to lessen the perceptions of social isolation or increase social support. Future research might also include studies to compare the effects of face to face groups with virtual groups on perceptions of social isolation and social support, and/or peer-led groups compared to groups led by a trained facilitator on those same perceptions.

Contribution of Research to Science and Nursing

Nursing research is sparse on the experience of living with a rare disease (Wagner, Christensen, & Coleman, 2015), and is even more lacking on the concept of social isolation in the rare disease population, although recent studies are beginning to address this gap (Garrino et al., 2015; Hoth et al., 2014; Wienke et al., 2014). This dissertation contributes to the science of nursing by calling attention to this need, and by highlighting some of the gaps in the published literature on social isolation and social support in two rare lung diseases. The findings from this study contribute to current knowledge by identifying similarities and differences that exist between two similar, yet distinct populations in terms of not only the perceptions of both of these phenomena, but

the different ways in which individuals seek support. Findings further suggest that there is a need to explore the framework from which that support stems, whether via established organizations such as the Alpha-1 Foundation, or more peer-based support groups, such as Facebook chat rooms and the like. Finally, this study addressed the alpha-1 and sarcoidosis populations, isolating issues in these populations.

Although the generalizability of the findings from this exploratory study is limited, the study design and results are valuable. Depending upon the condition, a rare disease population can be geographically dispersed. In the case of the ultra-rare diseases, there may be only a few documented cases. By utilizing the power of the internet, combined with existing resources such as the MUSC registry coordinator, this study's investigators were able to enroll a sample of subjects from across the United States, with diverse demographics. Although this is a limitation as mentioned previously, this also provides evidence to support the utility of this approach. No longer are researchers confined by brick and mortar walls. Indeed, some of the ultra-rare conditions are utilizing a virtual approach to collect data. Marshall-Smith Syndrome is a condition that is known to affect approximately fifty people worldwide. A global collaboration using an online wiki to facilitate data collection and sharing has brought together clinicians and scientists to harness the power of the group(Shaw et al., 2010). This dissertation study and other studies, similar to the Shaw study, provide compelling evidence to support such non-traditional approaches. Establishment of such registries is not new to the alpha-1 community. By 2005, following the recommendation of the World Health Organization, the Alpha One International Registry included 21 countries on four continents, and is now the largest α1-antitrypsin deficiency registry in the world, with > 4,000 patients

(Gupta, Bayoumi, & Faughnan, 2011). The registry has facilitated epidemiologic as well as interventional studies, and is similar to the MUSC Alpha-1 Registry from which subjects for this study were recruited. In the future, scientists and other clinicians may find the virtual approach used by this dissertation study to be useful when considering how best to collect information from their own populations of interest.

The results of this study may be of particular interest to organizations representing rare disease groups, especially the results which suggest that an organized framework and some measure of shepherding by peers or other navigators could prove beneficial to patients, especially at the initial diagnosis. The use of peer-navigators has been explored in a variety of conditions, including chronic obstructive pulmonary disease (COPD), spinal cord injury, and breast cancer (Mollica, Nemeth, Newman, Mueller, & Sterba, 2014; Newman et al., 2014; Thomashow et al.). Registries that maintain large numbers of patients with a given condition have also shown to be useful in contributing to current and future studies(Strange et al., 2015). By encouraging the nurse scientists of today to think "out of the box" in anticipation of tomorrow, future work can truly build on the efforts of our predecessors.

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ADDITIONAL TABLES OF INTEREST TO SUPPORT DISSERTATION STUDY

Table 1 Demographic Characteristics of Pooled Study Population and By Condition				
	All, (n=244)	**Alpha-1, (n=177)**	**Sarcoidosis, (n=67)**	**p-value**
Age, mean (sd)	56.6 (11.4)	59.4 (11.4)	50.1 (8.3)	<0.001
Gender, n (%)				
Male	76(31.5)	65(37.4)	11(16.4)	0.002
Female	165(68.5)	109(62.6)	56(83.6)	
Marital status, n (%)				
Married	154(64.7)	113(65.7)	41(62.1)	0.317
Single	17(7.1)	12(7.0)	5(7.6)	
Divorced	43(18.1)	27(15.7)	16(24.2)	
Widowed	7(2.9)	7(4.1)	0	
Partnered	17(7.1)	13(7.6)	4(6.1)	
Living situation, n (%)				
Alone	39(16.2)	32(18.4)	7(10.4)	0.003
With spouse/life partner	117(48.5)	93(53.4)	24(35.8)	
With children	16(6.6)	7(4.0)	9(13.4)	
With spouse/life partner & children	54(22.4)	33(19.0)	21(31.3)	
With a friend	5(2.1)	2(1.1)	3(4.5)	
Other	10(4.1)	7(4.0)	3(4.5)	
Annual household income (per year)				
<$10,000	15(6.8)	10(6.1)	5(8.6)	0.829
$10,000-$24,999	34(15.4)	24(14.7)	10(17.2)	
$25,000-$49,999	58(26.2)	42(25.8)	16(27.6)	
$50,000-$99,999	81(36.7)	63(38.7)	18(31.0)	
$100,000+	33(14.9)	24(14.7)	9(15.5)	
Ethnicity				
Hispanic, Latino/a or Spanish origin	14(5.8)	8(4.5)	6(9.1)	0.216
Not of Hispanic, Latino/a or Spanish origin	228(94.2)	168(95.5)	60(89.6)	
Race				
White	226(93.0)	173(98.3)	53(79.1)	<0.001
Black or African American	11(4.5)	1(0.6)	10(14.9)	
American Indian or Alaska Native	1(0.4)	0	1(1.5)	
Asian Indian	1(0.4)	0	1(1.5)	
Other	4(1.6)	1(0.6)	3(4.5)	
Prefer not to say	1 (0.4)	1 (0.6)	0	

Table 2 Clinical Characteristics: Pooled Study Population and By Condition				
	All, (n=244)	**Alpha-1, (n=177)**	**Sarcoidosis, (n=67)**	**p-value**
Genotype (alpha-1), n(%)				
ZZ		97(55.7)		
SZ		18(10.3)		
SS		5(2.9)		
MZ		32(18.4)		
MS		1(0.6)		
Other		11(6.3)		
I don't know		10(5.7)		
Severity (sarcoidosis), n(%)				
Stage 1			3(4.6)	
Stage 2			5(7.7)	
Stage 3			9(13.8)	
Stage 4			9(13.8)	
I don't know			39(60.0)	
MRC Dyspnea Score, n(%)				
0	27(11.3)	19(10.9)	8(12.3)	0.634
1	82(34.2)	64(36.6)	18(27.7)	
2	97(40.4)	66(37.7)	31(47.7)	
3	26(10.8)	20(11.4)	6(9.2)	
4	8(3.3)	6(3.4)	2(3.1)	
MRC Dyspnea Score, median(IQR)	2(1-2)	2(1-2)	2(1-2)	0.657
MRC Dyspnea Score, mean (sd)	1.6(0.9)	1.6(0.9)	1.6(0.9)	
Number of years with condition, median(IQR)	7(3-13)	7(3-14)	6(3-12)	0.347
Number of years with condition, mean (sd)	10.0(10.7)	10.4(11.4)	8.8(8.7)	
Family history of condition, n(%)	105(53.8)	98(70.0)	7(12.7)	<0.001
Deaf or serious hearing difficulty, n(%)	18(7.4)	12(6.8)	6(9.0)	0.588
Blind or serious difficulty seeing, n(%)	23(9.5)	11(6.3)	12(17.9)	0.006
Difficulty concentrating, remembering or making decisions, n(%)	71(29.7)	37(21.5)	34(50.7)	<0.001
Difficulty walking or climbing stairs, n(%)	149(61.3)	110(62.5)	39(58.2)	0.539
Difficulty dressing or bathing, n(%)	71(29.3)	55(31.3)	16(24.2)	0.286
Difficulty doing errands alone, n(%)	88(36.2)	57(32.4)	31(46.3)	0.044
Number days (in past 30) pain made usual activities hard, median (IQR)	2(0-20)	0(0-10)	18(2-30)	<0.001
Number days (in past 30) pain made usual activities hard, mean (sd)	9.4(11.9)	6.6(10.4)	16.7(12.8)	
Number days (in past 30) fatigue made usual activities hard, median (IQR)	15(3-30)	10(2-30)	20(10-30)	0.005
Number days (in past 30) fatigue made usual activities hard, mean (sd)	15.8(13.9)	14.6(14.7)	18.7(11.2)	
Number times (in past 7days) left house or apartment median (IQR)	5(3-7)	5(3-9)	4(2-7)	0.012
Number times (in past 7days) left house or apartment, mean (sd)	6.6(5.8)	7.1(6.2)	5.0(4.4)	
Participates in face to face support groups, n(%)	55(22.8)	46(26.3)	9(13.6)	0.037
Number participated in in past year, median(IQR)	4(2.8-6.0)	4(3-5)	6(1-12)	0.578
Number participated in in past year, mean (sd)	4.8(3.7)	4.5(3.3)	6.3(5.2)	
Participates in online support groups, n(%)	107(44.4)	49(28.0)	58(87.9)	<0.001
Participates in advocacy groups	56(23.2)	41(23.3)	15(23.1)	0.972
Groups/activities participated in outside the home				
Church	73(29.9)	50(28.2)	23(34.3)	0.356
School/school groups	23(9.4)	14(7.9)	9(13.4)	0.188
Sport	51(20.9)	45(25.4)	6(9.0)	0.005
Book clubs	11(4.5)	9(5.1)	2(3.0)	0.732
Social clubs	38(17.5)	31(17.5)	7(10.4)	0.175
Other	89(36.5)	70(39.5)	19(28.4)	0.106
None	75(30.7)	52(29.4)	23(34.3)	0.455

Table 3 Ease of Completion of Friendship Scale and MOS-SSS				
	All N=244	**Alpha-1 N=177**	**Sarcoidosis N=64**	**p-value**
Friendship Scale*				
Very easy to complete	130(53.9)	97(55.4)	33(50.0)	0.091
Easy to complete	86(35.7)	65(37.1)	21(31.8)	
Hard to complete	23(9.5)	12(6.9)	11(16.7)	
Very hard to complete	2(0.8)	1(0.6)	1(1.5)	
MOS-SSS**				
Very easy to complete	129(54.0)	98(56.3)	31(47.7)	0.009
Easy to complete	84(35.1)	64(36.8)	20(30.8)	
Hard to complete	25(10.5)	12(6.9)	13(20.0)	
Very hard to complete	1(0.4)	0	1(1.5)	

Table 4	**Average Friendship Scale and Medical Outcomes Scale – Social Support Survey (MOS-SSS) by Study Population and Condition**								
	All, (n=244)		**Alpha-1, (n=177)**		**Sarcoidosis, (n=67)**		**W**	**Z**	**p-value**
	Mean (*95% CI)*	Median *(IQR)*	Mean *(95% CI))*	Median *(IQR)*	Mean (*95% CI)*	Median *(IQR)*			
Friendship Scale	16.3 (15.5-17.1)	17 (12-22)	17.0 (16.1-17.9)	18 (13-22)	14.5 (12.9-16.1)	15 (9-20)	6682.5	-2.595	0.009
MOS-SSS emotional/ informational support	27.3 (26.1-28.4)	29 (21-34)	28.1 (26.8-29.4)	30 (21-35.5)	25.0 (22.9-27.1)	24 (20-32)	6761.5	-2.427	0.015
MOS-SSS tangible support	14.2 (13.5-14.8)	16 (10-20)	14.5 (13.7-15.3)	16 (10-20)	13.3 (11.9-14.6)	14 (8-18.3)	7089.5	-1.821	0.069
MOS-SSS positive social interaction	11.2 (10.7-11.6)	12 (8-15)	11.5 (11.0-12.0)	12 (9-15)	10.3 (9.3-11.3)	12 (6.5-15)	6740.0	-2.096	0.036
MOS-SSS affectionate support	11.6 (11.1-12.1)	13 (9-15)	11.8 (11.2-12.4)	13.5 (9-15)	10.9 (9.9-12.0)	12 (7-15)	6916.5	-1.504	0.133
MOS-SSS Transformed total	63.8 (60.3-67.3)	68.4 (42.1-85.5)	66.4 (62.4-70.5)	73.7 (47.4-88.2)	56.9 (50.0-63.7)	62.5 (35.2-75.0)	5975.0	-2.481	0.013

Table 5	**Friendship Scale and Medical Outcomes Scale – Social Support Survey (MOS-SSS) by Study Population and Condition by Access to Support**						
	Accessed support		**Did not access support**		**W**	**Z**	**p-value**
	Mean(*95% CI)*	Median *(IQR)*	Mean*(95% CI))*	Median *(IQR)*			
All respondents							
Total, N	**134**		**108**				
Friendship Scale	15.9 (14.8-17.0)	17 (11-21.5)	16.9 (15.7-18.0)	18 (13-22)	15256.5	-1.211	0.226
MOS-SSS emotional/ informational support	26.8 (25.4-28.3)	27 (21-33)	27.8 (26.0-29.6)	30.5 (20-37)	15087.0	-0.958	0.338
MOS-SSS tangible support	14.2 (13.3-15.1)	15 (11-19)	14.2 (13.1-15.3)	16 (9-20)	15589.5	-0.354	0.723
MOS-SSS positive social interaction	10.9 (10.3-11.6)	12 (8-15)	11.4 (10.7-12.1)	12 (9-15)	14922.5	-0.933	0.351
MOS-SSS affectionate support	11.6 (10.9-12.3)	13 (8.5-15)	11.6 (10.9-12.4)	13 (9-15)	15080.5	-0.157	0.875
MOS-SSS Transformed total	63.0 (58.3-67.6)	68.4 (41.8-83.2)	64.9 (59.4-70.4)	69. (43.4-90.8)	13930.5	-0.635	0.526
Alpha-1							
Total, N	**75**		**100**				
Friendship Scale	17.4 (16.1-18.7)	19 (13-22)	16.7 (15.5-17.9)	17 (13-21.5)	8153.5	-0.734	0.463
MOS-SSS emotional/ informational support	28.6 (26.7-30.5)	30 (22.5-34.5)	27.7 (25.9-29.6)	30.5 (19.8-36.3)	8270.5	-0.493	0.622
MOS-SSS tangible support	15.1 (13.9-16.2)	16 (12-20)	14.2 (13.0-15.3)	16 (9-20)	8198.0	-0.877	0.380
MOS-SSS positive social interaction	11.7 (10.9-12.5)	12 (9-15)	11.4 (10.6-12.1)	12 (9-15)	7963.0	-1.104	0.270
MOS-SSS affectionate support	12.2 (11.4-13.1)	15 (10-15.0)	11.5 (10.8-12.3)	12 (9-15)	8004.5	-0.505	0.614
MOS-SSS Transformed total	68.7 (62.8-74.5)	75 (52.6-88.6)	64.7 (59.0-70.5)	66.4 (43.1-90.1)	7319.0	-0.754	0.451
Sarcoidosis							
Total, N	**59**		**8**				
Friendship Scale	13.9 (12.2-15.6)	14.4 (9-20)	18.9 (13.7-24.1)	22.5 (13.8-23)	1836.5	-2.096	0.036
MOS-SSS emotional/ informational support	24.5 (22.3-26.7)	24 (20-30.5)	28.6 (19.4-37.8)	31 (20-39.3)	1888.5	-1.072	0.284
MOS-SSS tangible support	13.1 (11.7-14.4)	13.5 (8-18)	14.8 (9.1-20.4)	17.5 (7.3-20)	1893.0	0.988	0.323
MOS-SSS positive social interaction	10.0 (9.0-11.1)	11.5 (6-13.5)	12.4 (9.5-15.4)	12 (12-15)	1759.0	-1.275	0.202
MOS-SSS affectionate support	10.7 (9.5-11.78)	12 (7-15)	12.9 (10.3-15.5)	14 (12-15)	1845.5	-1.476	0.140
MOS-SSS Transformed total	55.6 (48.3-62.86)	57.9 (34.2-75.0)	67.1 (38.7-94.5)	73.7 (43.4-96.1)	1679.5	-1.18	0.238

Table 6 Logistic Regression Analyses: Association between Demographic Characteristics and Perceived Social Isolation						
	Isolated, n(%)	**OR**	**95% CI**	**Wald**	**df**	**p-value**
Age		0.96	0.94-0.99	8.37	1	0.004
Gender						
Male	33(43.4)	1		6.92	1	0.009
Female	100(61.7)	2.10	1.21-3.66			
Marital Status						
Married	71(47.0)	1		14.66	4	0.005
Single	13(76.5)	3.66	1.14-11.74			
Divorced	33(76.7)	3.72	1.71-8.08			
Widowed	3(42.9)	0.85	0.18-3.91			
Partnered	9(52.9)	1.27	0.46-3.46			
Living situation						
Not alone	105(52.5)	1		4.75	1	0.029
Alone	28(71.8)	2.30	1.09-4.88			
Annual household income (per year)						
<$10,000	11(78.6)	1		19.25	4	0.001
$10,000-$24,999	27(79.4)	1.05	0.23-4.83			
$25,000-$49,999	38(65.5)	0.52	0.13-2.07			
$50,000-$99,999	34(42.5)	0.20	0.05-0.78			
$100,000+	14(43.8)	0.21	0.05-0.91			
Ethnicity						
Hispanic, Latino/a or Spanish origin	7(53.8)	1		0.01	1	0.715
Not of Hispanic, Latino/a or Spanish origin	124(55.4)	1.06	0.35-3.26			
Race						
White	123(55.2)	1				
Non-white	9(60.0)	1.22	0.42-3.542	0.13	1	0.653

Table 7 Logistic Regression Analyses: Associations between Clinical Characteristics and Perceived Social Isolation

	Isolated, n(%)	OR	95% CI	Wald	df	p-value
Condition						
Alpha-1	90(52.0)	1		3.30	1	0.069
Sarcoidosis	43(65.2)	1.72	0.96-3.10			
Genotype						
ZZ	49(51.6)	1		2.03	3	0.567
SZ	9(50.0)	0.94	0.34-2.57			
MZ	19(59.4)	1.37	0.61-3.09			
MS/SS/Other	6(37.5)	0.56	0.19-1.67			
Severity						
Stage 1 or 2	3(37.5)	1		4.49	1	0.034
Stage 3 or 4	14(82.4)	7.78	1.17-51.92			
MRC Dyspnea Score						
0	14(51.9)	1		11.16	3	0.010
1	34(44.4)	0.74	0.31-1.78			
2	54(57.4)	1.25	0.53-2.96			
3 or 4	27(79.4)	3.58	1.17-11.01			
Blind or serious difficulty seeing						
No	115(53.2)	1		4.31	1	0.038
Yes	17(77.3)	2.99	1.06-8.38			
Difficulty concentrating, remembering or making decisions,						
No	70(42.4)	1		29.7	1	<0.001
Yes	59(84.3)	7.28	3.57-14.86			
Difficulty walking or climbing stairs						
No	35(37.6)	1		19.33	1	<0.001
Yes	98(67.1)	3.38	1.97-5.83			
Difficulty dressing or bathing						
No	83(49.1)	1		10.45	1	0.001
Yes	50(72.5)	2.73	1.48-5.01			
Difficulty doing errands alone						
No	68(44.7)	1		19.17	1	<0.001
Yes	65(75.7)	3.65	2.04-6.52			
Number days (in past 30) pain made usual activities hard		1.07	1.04-1.10	23.6	1	<0.001
Number days (in past 30) fatigue made usual activities hard		1.06	1.04-1.09	27.12	1	<0.001
Number days (in past 7) left house or apartment		0.92	0.87-0.96	12.03	1	0.001
Participates in online support groups						
No	71(54.2)	1		0.27	1	0.606
Yes	61(57.5)	1.15	0.68-1.92			
Participates in face to face support groups						
No	107(58.8)	1		3.01	1	0.083
Yes	25(45.5)	0.58	0.32-1.07			
Participates in advocacy groups						
No	103(56.9)	1		0.823	1	0.364
Yes	28(50.0)	0.757	0.42-1.38			
Participates in Groups/activities participated in outside the home						
No	55(76.4)	1		16.88	1	<0.001
Yes	78(46.7)	0.271	0.15-0.51			

Table 8 Logistic Regression Analyses: Associations between Demographic Characteristics and Social Support

	Low-normal social support n(%)	OR	95% CI	Wald	df	p-value
Age		0.97	0.94-1.00	4.78	1	0.029
Gender						
Male	46(65.7)	1		5.15	1	0.023
Female	120(80.0)	2.09	1.11-3.94			
Marital Status						
Married	96(68.1)	1		10.30	4	0.036
Single	14(87.5)	3.28	0.72-15.05			
Divorced	37(92.5)	5.78	1.69-19.75			
Widowed	6(85.7)	2.81	0.33-24.06			
Partnered	9 (69.2%)	1.06	0.31-3.61			
Living situation						
Not alone	133(71.5)	1		5.84	1	0.016
Alone	34(91.9)	4.51	1.33-15.34			
Annual household income (per year)						
<$10,000	10(83.3)	1		10.45	4	0.033
$10,000-$24,999	28(90.3)	1.87	0.27-12.85			
$25,000-$49,999	46(85.2)	1.15	0.21-6.23			
$50,000-$99,999	49(66.2)	0.39	0.08-1.93			
$100,000+	22(68.8)	0.44	0.08-2.39			
Ethnicity						
Hispanic, Latino/a or Spanish origin	7(63.6)	1		0.73	1	0.394
Not of Hispanic, Latino/a or Spanish origin	158(75.2)	1.74	0.49-6.17			
Race						
White	155(74.9)	1		0.018	1	0.894
Non-white	11(73.3)	1.12	0.33-3.55			

Table 9 Logistic Regression Analyses: Associations between Clinical Characteristics and Social Support

	Low-normal social support n(%)	OR	95% CI	Wald	df	p-value
Condition						
Alpha-1	116(72.0)	1		2.44	1	0.118
Sarcoidosis	51(82.3)	1.80	0.86-3.76			
Genotype						
ZZ	65(74.7)	1		2.51	3	0.473
SZ	12(80.0)	1.35	0.35-5.25			
MZ	19(61.3)	0.54	0.23-1.28			
MS/SS/Other	10(71.4)	0.85	0.24-2.97			
Severity						
Stage 1 or 2	5(71.4)	1		0.353	1	0.553
Stage 3 or 4	14(82.4)	1.87	0.24-1465			
MRC Dyspnea Score						
0	17(77.3)	1		5.35	3	0.148
1	53(69.7)	0.678	0.22-2.06			
2	68(73.9)	0.833	0.28-2.50			
3 or 4	27(93.1)	3.97	0.69-22.82			
Family history of condition						
No	63(76.8)	1		1.24	1	0.265
Yes	68(69.4)	0.68	0.35-1.34			
Deaf or serious hearing difficulty						
No	154(74.8)	1		0.33	1	0.564
Yes	13(81.3)	1.46	0.40-5.34			
Blind or serious difficulty seeing						
No	150(73.9)	1		1.84	1	0.175
Yes	16(88.9)	2.28	0.63-12.71			
Difficulty concentrating, remembering or making decisions						
No	106(69.7)	1		6.40	1	0.011
Yes	57(86.4)	2.75	1.26-6.02			
Difficulty walking or climbing stairs						
No	60(70.6)	1		1.58	1	0.209
Yes	107(78.1)	1.49	0.80-2.76			
Difficulty dressing or bathing						
No	112(72.7)	1		2.19	1	0.139
Yes	55(82.1)	1.72	0.84-3.53			
Difficulty doing errands alone						
No	101(70.6)	1		4.44	1	0.035
Yes	66(83.5)	2.11	1.05-4.23			
Number days (in past 30) pain made usual activities hard		1.04	1.01-1.07	6.02	1	0.014
Number days (in past 30) fatigue made usual activities hard		1.06	1.03-1.09	13.84	1	<0.001
Number days (in past 7) left house or apartment		0.96	0.91-1.01	2.10	1	0.148
Participates in online support groups						
No	85(70.2)	1		3.20	1	0.074
Yes	80(80.8)	1.78	0.95-3.36			
Participates in face to face support groups						
No	128(76.2)	1		0.54	1	0.464
Yes	37(71.2)	0.77	0.38-1.55			
Participates in advocacy groups						
No	126(74.6)	1		0.08	1	0.782
Yes	39(76.5)	1.11	0.53-2.31			
Participates in Groups/activities participated in outside the home						
No	60(88.2)	1		8.57	1	0.003
Yes	107(69.0)	0.297	0.13-0.67			

Table 10 Reliability of Friendship Scale and MOS-SSS: By Study Population and Disease Condition			
	All Cronbach's α	**Alpha-1, Cronbach's α**	**Sarcoidosis, Cronbach's α**
Friendship scale	0.915	0.912	0.920
MOS-SSS emotional/ informational support	0.961	0.962	0.953
MOS-SSS tangible support	0.960	0.959	0.961
MOS-SSS positive social interaction	0.961	0.964	0.959
MOS-SSS affectionate support	0.964	0.960	0.971
MOS-SSS Transformed total	0.974	0.973	0.973

Table 11 Convergent Validity		
	Correlation with Friendship Scale, r	**p-value**
MOS-SSS emotional/ informational support	0.737	<0.001
MOS-SSS tangible support	0.598	<0.001
MOS-SSS positive social interaction	0.611	<0.001
MOS-SSS affectionate support	0.713	<0.001
MOS-SSS Transformed total	0.760	<0.001

LIST OF APPENDICES

Appendix A MUSC IRB APPROVAL LETTERS (INITIAL PROTOCOL AND AMENDMENT 1)

Institutional Review Board for Human Research (IRB)
Office of Research Integrity (ORI)
Medical University of South Carolina

Harborview Office Tower
19 Hagood Ave., Suite 601, MSC857
Charleston, SC 29425-8570
Federal Wide Assurance # 1888

APPROVAL:
This is to certify that the research proposal **Pro00039793** entitled:
A Mixed Methods Study of Social Isolation and Social Support in Alpha-1 Antitrypsin Deficiency and Sarcoidosis

Submitted by: **Susan Flavin**
Department: **Medical University of South Carolina**

For consideration has been reviewed by **IRB-I - Medical University of South Carolina** and approved with respect to the study of human subjects as adequately protecting the rights and welfare of the individuals involved, employing adequately methods of securing informed consent from these individuals and not involving undue risk in the light of potential benefits to be derived therefrom. Additionally, the Institutional Review Board for Human Research (IRB) recommends approval of the investigator's request for Waiver of Signed Consent in accordance with 45 CFR 46.117(c)(1),(2) because the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality and/or because the research presents no more than minimal risk and involves no procedures for which written consent is normally required outside of the research context. The Institutional Review Board for Human Research (IRB) also recommends approval of the investigator's request for a HIPAA Waiver of Authorization, as it appears that the criteria of the Privacy Rule have been satisfied. The HIPAA Waiver of Authorization was reviewed under expedited review procedures. No IRB member who has a conflicting interest was involved in the review or approval of this study, except to provide information as requested by the IRB.

Original Approval Date: **1/28/2015**
Approval Expiration: **1/27/2016**

Type: **Expedited**

Chairman, **IRB-I - Medical University of South Carolina**
Mark Hamner*

Statement of Principal Investigator:

As previously signed and certified, I understand that approval of this research involving human subjects is contingent upon my agreement:

1. To report to the Institutional Review Board for Human Research (IRB) any adverse events or research related injuries which might occur in relation to the human research. I have read and will comply with IRB reporting requirements for adverse events.
2. To submit in writing for prior IRB approval any alterations to the plan of human research.
3. To submit timely continuing review reports of this research as requested by the IRB.
4. To maintain copies of all pertinent information related to the research activities in this project, including copies of informed consent agreements obtained from all participants.
5. To notify the IRB immediately upon the termination of this project, and/or the departure of the principal investigator from this Institution and the project.

* ***Electronic Signature****: This document has been electronically signed by the IRB Chairman through the HSSC eIRB Submission System authorizing IRB approval for this study as described in this letter.*

Institutional Review Board for Human Research (IRB)
Office of Research Integrity (ORI)
Medical University of South Carolina

Harborview Office Tower
19 Hagood Ave., Suite 601, MSC857
Charleston, SC 29425-8570
Federal Wide Assurance # 1888

APPROVAL: **Protocol: MS2_Pro00039793**
MUSC Amendment # Ame2_Pro00039793
Amendment Title Amendment 2 for IRB Study #Pro00039793

This is to certify that the amendment to the research proposal entitled:
A Mixed Methods Study of Social Isolation and Social Support in Alpha-1 Antitrypsin Deficiency and Sarcoidosis

and submitted by: **Susan Flavin**
Department: **Medical University of South Carolina**
Sponsor:

for consideration has been reviewed by **IRB-I - Medical University of South Carolina** and approved with respect to the study of human subjects as adequately protecting the rights and welfare of individuals involved, employing adequate methods of securing informed consent from these individuals and not involving undue risk in the light of potential benefits to be derived therefrom. No IRB member who has a conflicting interest was involved in the review or approval of this amendment, except to provide information as requested by the IRB. If this amendment required a change in the currently approved informed consent, then all previous consents should be marked obsolete.

Approval Date: **4/23/2015**

Amendment Type: **Expedited**

Chair, **IRB-I - Medical University of South Carolina**
Mark Hamner∗

∗ ***Electronic Signature****: This document has been electronically signed by the IRB Chairman through the HSSC eIRB Submission System authorizing IRB approval for this study as described in this letter.*

Appendix B IRB-Approved Information for Survey Participants Document

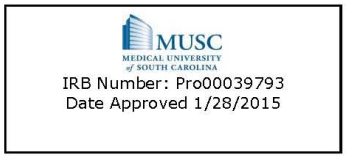
INFORMATION FOR SURVEY PARTICIPANTS
STATEMENT OF RESEARCH

You are being asked to volunteer for a research study. This research study is being done by Susan Flavin, MSN, RN a doctoral student at the Medical University of South Carolina College of Nursing.

Purpose of the research: The purpose of this study is to gather information about feelings of social isolation and social support in people who have one of two types of lung disease, alpha-1 antitrypsin deficiency or sarcoidosis. You are being asked to participate in this study because you either alpha-1 or sarcoidosis. The main goal is to use the information from this project to help identify, develop, and offer programs that may help with feelings of social isolation, and/or social support for people with these rare lung diseases. Findings from this study may help us learn about things that help you to stay healthy, feel connected to others and to participate fully in the community. Up to 150 volunteers are expected to take part in this study.

What you will do in this research: If you decide to participate, you will be asked to complete an online survey. The questions in the survey will address topics including: information about you and your disease including background (age, living situation, length of time that you've had your disease, education, any impairments that you might have as a result of your disease, etc), your feelings of social isolation (feeling apart from the community), your feelings about the availability of social support, and how much shortness of breath you may experience as a result of your condition. You may also be asked to participate in a brief (~30 minute) interview in person, by phone, or via the computer (for example, via Skype).

Time required: The survey will take approximately 20-40 minutes to complete. If you participate in the interview, this will last approximately 30 minutes.

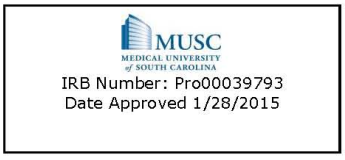


Risks: Taking part in the study should not put you at risk for physical harm. You may feel uncomfortable answering certain questions about aspects of either alpha-1 or sarcoidosis. You are not required to answer any questions that make you feel uncomfortable. Should you choose to complete the survey online, there is a potential for loss of privacy if you do not click on "save and return later" or "submit" or close the survey before leaving the computer. To minimize this risk, the only identifier on the survey itself will be your survey ID number. Despite these measures and all efforts to ensure security, there still is some risk of loss of confidentiality of personal information since the investigator will have some of your health information, including first name, last initial, and your diagnosis.

Benefits: There will be no direct benefit to you from participating in this study. However, it is hoped that the information gained from the study will help in the treatment of other people with alpha-1, sarcoidosis, or other rare lung diseases. This study will help us learn more what you experience in terms of social isolation and social support, and may allow us to think about how to develop interventions that will help to maintain your health and increase your ability to participate in the community as an individual with a rare lung disease.

Payment for participation: If you are interested, you can decide to enter a drawing for the chance to win an Apple iPad as compensation for your participation. If interested, you will be requested to enter your contact email at the end of the REDCap survey. One random email will be chosen at the conclusion of enrollment and the iPad given to that respective subject. You are not required to enter the drawing to participate in the study.

Confidentiality: To protect your confidentiality, you have been assigned a survey identification number that will be the only link between you and the information you



provide in the survey. This ID number will only be used to track who has returned the survey and provide compensation. To keep your information safe, the online surveys are stored in a secure computer database. The researchers will enter study data on a computer, which is password-protected, and use special coding to protect the information. We plan to publish the results of this study, but will not include any information that would identify you.

Participation and withdrawal: Your participation is completely voluntary, and you may quit at any time. You may also skip any question, but continue to complete the rest of the survey. Participation in this study will not affect your relationship with any patient groups that you might participate in, or MUSC, if your physician is located at MUSC.

To Contact the Researcher: If you have questions or concerns about this research, please contact:
Susan Flavin, MSN, RN at the Medical University of South Carolina, College of Nursing
Phone: 610-570-2919 **Email:** flavin@musc.edu

If you have any questions, problems, or concerns, desire further information or wish to offer input, you may contact the Medical University of SC Institutional Review Board for Human Research IRB Manager or the Office of Research Integrity Director at (843) 792-4148. This includes any questions about your rights as a research subject in this study. Please keep this information sheet for your records.

IRB Number: Pro00039793
Date Approved 1/28/2015

Appendix C IRB-Approved Recruitment Flyer

MUSC
COLLEGE of NURSING

VOLUNTEERS WANTED FOR A RESEARCH STUDY

A Mixed Methods Study of Social Isolation in Alpha-1 Antitrypsin Deficiency and Sarcoidosis

We are conducting a research study in individuals who have sarcoidosis or alpha-1 antitrypsin deficiency, and who have lung involvement as a result of either one of these conditions. The purpose of this research study is to investigate the feelings of social isolation and social support that people who have either one of these conditions experience.

To be eligible for this research study you must:

- Be an adult, aged 18 years or older
- Be able to confirm that a physician diagnosed you with either alpha-1 antitrypsin deficiency or sarcoidosis
- Have lung involvement as a result of your condition
- Be able to read and speak English
- Have access to a computer with a valid email address (for purposes of completing instruments via the internet, on a secure site)

CONTACT INFORMATION

To find out more about this study, please contact Susan Flavin, MSN, RN at flavin@musc.edu OR 610-570-2919

Participation in this study involves:

- A one-time completion of 4 questionnaires and 4 individual questions on a secure electronic site on the internet (~20-30 minutes to complete)
- All participants will be asked to participate in one-on-one interviews via phone, via the computer (Skype or a similar program) or face-to-face (where logical and appropriate) (approximately 30-45 minutes)
    - Your eligibility for the study does not require that you participate in the interview.

- Interested participants will be eligible to participate in a drawing for an Apple iPad. One iPad will be given away to one participant in the study.

Taking part in the study should not put you at risk for physical harm. You may feel uncomfortable answering certain questions about aspects of having your condition. There will be no direct benefit to you from participating in this study. It is hoped that the information gained from the study will help in the treatment of other people with sarcoidosis, alpha-1 antitrypsin deficiency, or other rare diseases.

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

IRB Number: Pro00039793

Date Approved 1/28/2015

Appendix D Letters of Support from NORD and INSPIRE

NORD
National Organization for Rare Disorders

January 12, 2015

Susan Flavin, MSN, RN
Doctoral Candidate
Medical University of South Carolina
College of Nursing
c/o Susan Flavin
132 Barton Drive
Spring City, PA 19475

Dear Ms. Flavin,

On behalf of the NORD (National Organization for Rare Disorders) community, I am writing to confirm support recruitment for your research study on the perceptions of social isolation and social support of people with the rare lung diseases of sarcoidosis and alpha-1 antitrypsin deficiency by posting information on our website and/or in our social media, once you have received approval from your university's IRB.

The National Organization for Rare Disorders (NORD) is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

We wish you much success with your study.

Sincerely,

Mary Dunkle

Mary Dunkle
Vice President, Educational Initiatives

55 Kenosia Avenue • Danbury, CT 06810
T 203.744.0100 • F 203.798.2291

1900 Crown Colony Drive, 4th Floor • Quincy, MA 02169
T 617.249.7300 • F 617.249.7301

1779 Massachusetts Ave. NW, Suite 500 • Washington, DC 20036
T 202.588.5700 • F 202.588.5701
rarediseases.org • orphan@rarediseases.org

January 6, 2015

Susan Flavin, MSN, RN
Doctoral Candidate
Medical University of South Carolina
College of Nursing
c/o Susan Flavin
132 Barton Drive
Spring City, PA 19475

Dear Ms. Flavin:

On behalf of Inspire, I am writing to confirm our support of your research study on the perceptions of social isolation and social support of people with the rare lung diseases of sarcoidosis and alpha-1 antitrypsin deficiency. In support of your study, we are willing to post in our online community information in support your research once you have received approval from your university's IRB.

With more than 100 national patient organization partnerships and over 500,000 members, Inspire has created the most authentic platform for patient engagement. We created Inspire with the belief that patient contributions to medical progress have been historically underappreciated, and great progress in medical research will result from involving patients and fully valuing their contributions. We are a privately-held company based in Princeton, NJ, that partners with organizations including the Ovarian Cancer National Alliance, National Osteoporosis Foundation, Arthritis Foundation, the Foundation for Sarcoidosis Research, National Psoriasis Foundation, and Genetic Alliance, to provide online patient communities in a safe, privacy-protected environment.

We are pleased that you reached out to us based upon our reputation for ethical patient engagement in various communities, including sarcoidosis and alpha-1 antitrypsin deficiency, your specific communities of interest.

We wish you much success with your study.

Sincerely,

Brian Loew
CEO
Inspire
174 Nassau St.
Princeton, NJ 08540

Inspire together we're better
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Appendix E Letters of Permission from Journal Editors to Use Published Papers in Compendium

International Journal of Caring Sciences September-December 2015 Volume 8 | Issue 3| Page 783

Special Article

Social Isolation and its Applicability to Persons with Sarcoidosis and Alpha-1 Antitrypsin Deficiency: A Dimensional Concept Analysis

Susan K. Flavin, MSN, RN, Doctoral Candidate
Medical University of South Carolina, Charleston, USA

Correspondence: Susan K. Flavin, MSN, RN, 132 Barton Drive, Spring City, PA 19475, USA
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From: IJCS Editorial Office [ijcseditorial@yahoo.com]
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Dear Ms Flavin,

You have my permission to use the full text of your article "Social Isolation and Its Applicability to Persons with Sarcoidosis and Alpha-1 Antitrypsin Deficiency: A Dimensional Concept Analysis", which appears in the latest issue of the International Journal of Caring Sciences (Volume 8, Issue 3), as part of your dissertation compendium.

I wish you good luck and every success in the defense of your dissertation.

Professor Despina Sapountzi-Krepia
Publisher and Editor in Chief, International Journal of Caring Sciences

Int Public Health J 2015;7(3):255-270 ISSN: 1947-4989

Measurements of social isolation and social support for rare lung disease patients: An integrative review

Susan K Flavin, MSN, RN*
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Abstract

Social support is an integral component of health. The risk of social isolation and perceptions of minimal support are high for persons living with rare chronic lung diseases such

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Joav Merrick [Jmerrick@zahav.net.il]

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Good luck and all the best

Professor Joav Merrick, MD, MMedSci, DMSc
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Appendix F Demography Instrument (created by PI and refined by Dissertation Committee)

Demographic / Clinical Questionnaire

Age [Text Box]:	**Please enter your actual age (in years)_____**
Ethnicity*	**Are you Hispanic, Latino/a, or Spanish origin (one or more categories may be selected)**
	☐ No, not of Hispanic, Latino/a, or Spanish origin
	☐ Yes, Mexican, Mexican American, Chicano/a
	☐ Yes, Puerto Rican
	☐ Yes, Cuban
Race*	**What is your race?**
	☐ White
	☐ Black or African American
	☐ American Indian or Alaska Native
	☐ Asian Indian
	☐ Chinese
	☐ Filipino
	☐ Japanese
	☐ Korean
	☐ Vietnamese
	☐ Other Asian
	☐ Native Hawaiian
	☐ Guamanian or Chamorro
	☐ Samoan
	☐ Other Pacific Islander
	☐ Other
Disability status*	
During the past 30 days, for about how many days did pain make it hard for you to do your usual activities, such as self-care, work, or recreation? [TEXT BOX]	**___ days**
During the past 30 days, for about how many days did fatigue or being extremely tired make it hard for you to do your usual activities, such as self-care, work, or	**___ days**

Age [Text Box]:	**Please enter your actual age (in years)_____**
recreation? [TEXT BOX]	
Are you deaf or have serious difficulty hearing?	**☐Yes**
	☐ No
Are you blind or do you have serious difficulty seeing, even when wearing glasses?	**☐Yes**
	☐ No
Because of a physical, mental or emotional condition, do you have serious difficulty concentrating, remembering, or making decisions?	**☐Yes**
	☐ No
Do you have serious difficulty walking or climbing stairs?	**☐Yes**
	☐ No
Do you have difficulty dressing or bathing?	**☐Yes**
	☐ No
Because of a physical, mental, or emotional condition, do you have difficulty doing errands alone such as visiting a doctor's office or shopping?	**☐Yes**
How many times have you left your house/apartment in the past week?	**<Free text entry>**
	☐ No
Gender	**☐ Male**
	☐ Female
Marital Status	**☐ Married**
	☐ Single
	☐ Divorced

Age [Text Box]:	**Please enter your actual age (in years)_____**
	☐ Widowed
	☐ Partnered (in a committed relationship)
Living Situation	**☐ I live alone**
	☐ I live with a spouse / life partner
	☐ I live with my child/children
	☐ I live with spouse / life partner & child/children
	☐ I live with a friend
	☐ Other
Annual income in the home	**☐ < $10,000/year**
	☐ $10,000 - $24,999/year
	☐ $25,000 – $49,999/year
	☐ $50,000 – $99,999/year
	☐ ≥ $100,000/year
Number of years since diagnosis	**Enter actual number of years. If less than 1 year, enter "0": ____**
Condition	**☐ Alpha-1**
	☐ Sarcoidosis
Genotype (if alpha-1)	**☐ ZZ**
	☐ SZ
	☐ SS
	☐ MZ
	☐ MS
	☐ Do not know
Disease severity (if sarcoidosis)	**☐ Stage 1**
	☐ Stage 2
	☐ Stage 3
	☐ Stage 4
	☐ Do not know
Is another family member involved who has the disease	**☐ Yes**

Age [Text Box]:	**Please enter your actual age (in years)_____**
	☐ No
Do you participate in online support groups?	**☐ Yes**
	☐ No
Do you participate in face-to-face support groups?	**☐Yes**
	☐ No
If "yes", how many face-to-face support groups per year do you participate in?	**____ [free text box]**
Do you participate in any advocacy groups	**☐Yes**
	☐ No
Do you participate in any activities/groups outside of the home? (Check all that apply)	**☐ Church**
	☐ School / school groups
	☐ Sporting/physical activity
	☐ Book clubs
	☐ Social clubs
	☐ Other

*Categories adopted from Office of Minority Health. Final data collection standards for race, ethnicity,
primary language, sex, and disability status required by section 4302 of the Affordable Care Act. US Dept. of Health and Human Services. Accessed 20 Nov 2013: http: //minorityhealth.hhs.gov/templates/browse.aspx?lvl=2&lvlid=208.

Appendix G Friendship Scale

THE FRIENDSHIP SCALE[1]

During the <u>past four weeks</u>:

*1. It has been easy to relate to others:

- ☐ Almost always
- ☐ Most of the time
- ☐ About half the time
- ☐ Occasionally
- ☐ Not at all

2. I felt isolated from other people:

- ☐ Almost always
- ☐ Most of the time
- ☐ About half the time
- ☐ Occasionally
- ☐ Not at all

*3. I had someone to share my feelings with:

- ☐ Almost always
- ☐ Most of the time
- ☐ About half the time
- ☐ Occasionally
- ☐ Not at all

*4. I found it easy to get in touch with others when I needed to:

- ☐ Almost always
- ☐ Most of the time
- ☐ About half the time
- ☐ Occasionally
- ☐ Not at all

5. When with other people, I felt separate from them:

- ☐ Almost always
- ☐ Most of the time
- ☐ About half the time
- ☐ Occasionally
- ☐ Not at all

6. I felt alone and friendless:

- ☐ Almost always
- ☐ Most of the time
- ☐ About half the time
- ☐ Occasionally
- ☐ Not at all

* = These items reversed prior to scoring

Appendix H Instructions for Scoring Friendship Scale

FRIENDSHIP SCALE

.

Source: The items come from the 6-item Friendship Scale. Used with permission.

Reference: Hawthorne, G. (2006). Measuring social isolation in older adults: Development and initial validation of the Friendship Scale. *Social Indicators Rese*arch, 77, 521-548.

Scale Description: The Friendship Scale is a short, 6-item scale assessing social isolation.

Scoring and Algorithm

Note: For each assessment, there is an algorithm leading to one of three acuity ranges: Low, Moderate, or High. The logic for the user receiving specific feedback is included in the algorithms below.

Scoring and Algorithm

Each item is scored 0-4, as indicated below. Total is sum of all 6 items, possible range for total is 0-24.

For Questions #1, #3, #4 the items are scored:

Almost always = 4
Most of the time = 3
About half the time = 2
Occasionally = 1
Never = 0

Questions #2, #5, #6, the items are scored:

Almost always = 0
Most of the time = 1
About half the time = 2
Occasionally = 3
Never = 4

Algorithm

Total = 19-24 Friendship High Acuity
Total = 16-18 Friendship Moderate Acuity
Total = 0-15 Friendship Low Acuity

Appendix I Medical Outcomes Survey – Social Support Scale (MOS-SSS)

THE Medical Outcomes Survey (MOS) SOCIAL SUPPORT SURVEY

People sometime s look to others for companionship, assistance, or other types of support. How often is e ach of the following kinds of support available to you if you need it?
Circle one number on each line .

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
Emotional/informational support					
Someone you can count on to listen to you when you need to talk	1	2	3	4	5
Someone to give you information to help you understand a situation	1	2	3	4	5
Someone to give you good advice about a crisis	1	2	3	4	5
Someone to confide in or talk to about yourself or your problems	1	2	3	4	5
Someone whose advice you really want	1	2	3	4	5
Someone to share your most private worries and fears with	1	2	3	4	5
Someone to turn to for suggestions about how to deal with a personal problem	1	2	3	4	5
Someone who understands your problems	1	2	3	4	5
Tangible support					
Someone to help you if you were confined to bed	1	2	3	4	5
Someone to take you to the doctor if you needed it	1	2	3	4	5
Someone to prepare your meals if you were unable to do it yourself	1	2	3	4	5
Someone to help with daily chore s if you were sick	1	2	3	4	5
Affectionate support					
Someone who shows you love and affection	1	2	3	4	5
Someone to love and make you feel wanted	1	2	3	4	5
Someone who hugs you	1	2	3	4	5
Positive social interaction					
Someone to have a good time with	1	2	3	4	5
Someone to get together with for relaxation	1	2	3	4	5
Someone to do something enjoyable with	1	2	3	4	5
Additional item					
Someone to do things with to help you get your mind off things	1	2	3	4	5

Appendix J Instructions for Scoring the MOS-SSS

Medical Outcomes Study: Social Support Survey Scoring Instructions

How to score the survey

The survey consists of four separate social support subscales and an overall functional social support index. A higher score for an individual scale or for the overall support index indicates more support.

- To obtain a score for each subscale, calculate the average of the scores for each item in the subscale.
- To obtain an overall support index, calculate the average of (1) the scores for all 18 items included in the four subscales, and (2) the score for the one additional item (see last item in the survey).
- To compare to published means in the article referenced below, scale scores can be transformed to a 0 - 100 scale using the following formula:

$$100 \times \frac{\text{(observed score - minimum possible score)}}{\text{(maximum possible score - minimum possible score)}}$$

Appendix K The modified Medical Research Council (mMRC) Dyspnea Score

Level of Dyspnea	Grade
1. I only get breathless with strenuous exercise.	0
2. I get short of breath when hurrying on level ground or walking up a slight hill.	1
3. On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level	2
4. I stop for breath after walking about 100 yards or after a few minutes on level ground	3
5. I am too breathless to leave the house or I am breathless when dressing	4

Appendix L Study Protocol

Medical University of South Carolina
Protocol

PI Name: Susan Flavin, MSN, RN

Study Title: **A Mixed Methods Study of Social Isolation and Social Support in Alpha-1 Antitrypsin Deficiency and Sarcoidosis**

TABLE OF CONTENTS

A. SPECIFIC AIMS

The purpose of this parallel convergent mixed-methods study is to describe perceptions of the social impact of living with one of two rare diseases. The study will be guided by an interpretative phenomenological approach, using semi-structured interviews and quantitative measurement of perceived social isolation as measured by the Friendship Scale and perceived availability of social support as measured by the Medical Outcomes . Qualitative data will be obtained via interviews, transcribed, and analyzed via nVivo10. Quantitative data will be obtained via participant completion of the Friendship Scale and the MOS-SSS, coded and uploaded into SPSS v22 for analysis. Findings will be linked by a study ID number for comparison.
The rationale that underlies the proposed research is that prior to undertaking any large study to assess the presence and magnitude of perceived effect of living with a rare disease on social interactions, one must understand how it presents, what may ameliorate it, and what potential interventions might be useful.

SPECIFIC AIMS

Aim #1: To explore perceptions of the social impact of living with rare disease by assessing perceptions of social isolation, social support, connectedness, social participation and relationships in adults with two rare lung diseases, AATD and sarcoidosis, in an academic center and/or via the Web using one-on-one interviews.

Aim #2: To compare the Friendship Scale (Appendix 2) and the MOS-SSS (Appendix 3) in individuals who have ever accessed compared to never accessed a support group in Alpha-1 and Sarcoidosis. We will also evaluate these tools as measures of perceived social isolation and availability of social support, respectively.

Aim #3: Triangulate the survey and interview results to identify areas for development of interventions and preferences to improve individuals' preferred level of social interaction.

Expected Results: The results will reveal some degree of social isolation in both groups, and the isolation may be directly correlated with involvement in support groups (participation in online or face-to-face groups = decreased perceived social isolation and perceptions of increased social support).

Conclusion/Implications: The findings of the study will provide preliminary information useful for refining hypotheses related to perceived social isolation and social support in rare disease patients and to inform future intervention development.

B. BACKGROUND AND SIGNIFICANCE

Many rare diseases are chronic, complex and associated with physical, intellectual or neurological disabilities (Anderson, Elliott, & Zurynski, 2013). These conditions often accompany significant psychosocial and emotional impact for patients and families, compounded by a lack of support services. Functional limitations and the lack of support services can lead to perceptions of social isolation. Over the past three decades, social isolation as a variable has been shown to be predictive of mortality and morbidity in general population samples (House, 2001; House, Umberson, & Landis, 1988, Brummet, et al, 2001) and in studies of diseased populations, especially those suffering from cardiac disease (Berkman, 1995; Berkman & Syme, 1979). Insight into factors contributing to perceptions of social isolation can be useful in designing health promotion interventions (Berkman, 1995). Despite the number affected, rare disease patients often feel isolated and unable to get the information and support needed (Colledge & Solly, 2012). Few published studies explore the psychosocial impact of living with a rare disease (Wienke et al., 2014; Acorn, Joachim, & Wachs, 2003; Henderson, Packman, & Packman, 2009; Stoller, Smith, Yang, & Spray, 1994). No published studies on social isolation in rare diseases were identified, despite the fact that this phenomenon is repeatedly verbalized by individuals who suffer from both diseases (personal communications, M. Judson, 2012, W. Hunter, 2013) and the fact that individuals are encouraged to seek support (Lasker, Sogolow, & Sharim, 2005). Indeed, the authors of a recent study of the association between the social environment and uncertainty among a sample of patients with alpha-1 antitrypsin deficiency (AATD)-associated COPD have called for more work evaluating the impact of social isolation and loneliness on individuals with AATD(Hoth et al., 2014). The magnitude of perceived social impact of living with rare disease

and its presentation in these individuals remains unknown. The risk of social isolation may be high for persons with rare diseases such as sarcoidosis and alpha-1 antitrypsin deficiency (AATD).
The long-term goal of this study is to refine hypotheses related to the perceived effect of living with a rare disease on social interactions experienced by individuals with AATD and sarcoidosis and to inform future intervention development. The overall objective of this study is to gain insight into perceptions of the social impact, particularly social isolation and social support, and its consequences as experienced by individuals with AATD and sarcoidosis. The overarching question driving this proposal is: To what extent do individuals with the rare lung diseases of AATD and sarcoidosis perceive the social impact and consequences of living with these diseases as documented via participant self-report and as measured by the Friendship Scale and the Medical Outcomes Study – Social Support Survey (MOS-SSS). The rationale for this study is that results may yield information useful for refining hypotheses related to perceived social isolation and social support in rare diseases and to inform future intervention development.

An estimated 10% of Americans live with a diagnosis of one of the 6,000 to 8,000 known rare diseases (Griggs et al., 2009). The experience of living with a rare condition is complex and can significantly affect the individual's quality of life (Cohen & Biesecker, 2010). Many studies have adopted a population-based approach to rare diseases, but the patients' viewpoint on having such a disorder has remained unattended (Huyard, 2009). These patients can experience a myriad of psychosocial effects, including social stigma, lack of social support, and perceptions of social isolation. In general, social isolation is gaining increased attention as an integral component of health (World Health Organization, 2002) and the link between social isolation and health is one focus of the National Research Council's (National Research Council, 2001) interest in integrative health. Social isolation as a variable repeatedly showed a predictive relationship to mortality and serious morbidity both in general population samples (House, 2001; House, Umberson, & Landis, 1988) and in studies of diseased populations, especially those suffering from cardiac disease (Berkman, 1995; Berkman & Syme, 1979). In a recent review, (Cacioppo & Cacioppo, 2014) found that social isolation can have a negative impact on executive functioning, sleep, and mental and physical well-being, ultimately resulting in higher rates of morbidity and mortality.
Social support as "the individual belief that one is cared for and loved, esteemed and valued, and belongs to a network of communication and mutual obligations" (Cobb, 1976, p. 300). This too, can be lacking in individuals who suffer from rare diseases. Strategies to ameliorate perceptions of social isolation include various types of social support. The need for this is illustrated by the European Union Committee of Experts on Rare Diseases (EUCERD) in their investigation into the social support needs of individuals with rare diseases (2012). While the goal of this study is not to investigate the effect of interventions, the perceptions of social support are important to consider. As a first step, the perception of social support in these individuals is critical into moving further in this work.

Few published studies have explored the experiences of living with a rare disease; no published studies were identified that explored social isolation in rare lung diseases such as AATD or sarcoidosis. Two studies conducted in the rare disease of scleroderma identified social isolation as a phenomenon experienced by these individuals. Joachim & Acorn (2003) conducted a phenomenologic study to investigate the perspective of living with scleroderma and identified persistent themes of stigma and isolation. In their study of scleroderma patients, Cinar and colleagues (2012) found similar themes, including social isolation. Henderson and colleagues (2009) investigated the general psychosocial impact of living with Niemann Pick disease Type B, a rare lysosomal storage disorder; they also observed that those patients reported feelings of social isolation. McGarvey and Hart (2008) surveyed over 200 general practitioners in Ireland; they found that 72% of GPs agreed that having a rare disorder gives rise to additional family problems and 28% felt that rare disorders can result in feelings of isolation. No published studies have focused solely on the phenomenon of perceived social isolation in individuals living with rare diseases.

Similar results were found when seeking to identify published studies on perceived social support in either one of these conditions. No published studies were identified that explored perceived social support in sarcoidosis. No such studies were identified which investigated perceived social support in alpha-1 patients, although Hoth and colleagues (2014) found that in over 400 individuals with AATD, participation in support groups was associated with less ambiguity surrounding the disease. In particular, a statistically significant impact on ambiguity was found in those individuals who attended three or more support groups in the prior year compared with individuals who reported no such participation (b =−3.31, SE=1.29, p=0.010)

Recognition of the importance of research into rare lung diseases has been growing (Gupta, Bayoumi, & Faughnan, 2011). The contribution of the proposed research will explore and compare the perceptions of social isolation and social support in two rare lung disease groups from both the patient's perspective, as well as quantitatively measure the magnitude of the phenomenon.
Social isolation has been identified as a contributing factor for increased morbidity and mortality in various populations (Cacioppo & Hawkley, 2003; Cacioppo, Hawkley, Norman, & Berntson, 2011; Cornwell & Waite, 2009; Steptoe, Shankar, Demakakos, & Wardle, 2013). Despite confirmation of perceived social isolation in Internet chat rooms, support group meetings, and limited studies of rare disease patients (Black & Baker, 2011; Coulson, 2005; Coulson, Buchanan, & Aubeeluck, 2007; Lasker et al., 2005), there is a need for formal study that examines this phenomenon. The contribution of this study will be significant because it will provide baseline data that can be utilized to design larger studies in more diverse populations of rare disease patients, with the goal of developing and testing interventions that can enhance social support and ameliorate the condition of social isolation.

Despite the number of people affected by rare diseases, resources are lacking. Patients often feel isolated, unable to get the information and support they need (Colledge & Solly, 2012). The contribution of this research is aligned with the mission of the NINR, and specifically, the need to "develop strategies to assist individuals and their caregivers in managing chronic illness, including analyses of caregiver burden and cost-effectiveness" (National Institute of Nursing Research, 2011, p. 15). The contributions from this research will provide preliminary insights into the management of the social isolation component of these rare, chronic diseases. Findings from this study may be utilized to explore perceived social isolation and social support in other rare disease populations.

Current clinical practice approaches the management of rare diseases primarily from the biomedical approach, seeking to manage clinical physiologic symptoms (Budych, Helms, & Schultz, 2012). Less attention is given to the psychosocial management of the impact of these conditions. There remains little published evidence regarding the psychosocial burden of rare diseases (Acorn et al., 2003; Barrow, 2011; Feinberg, Law, Singh, & Wright; Huyard, 2009; Joachim & Acorn, 2003; McGarvey & Hart, 2008; Schieppati, Henter, Daina, & Aperia, 2008), and no identified studies have explored perceived social isolation in these individuals. As these patients may have significant needs and barriers to access to care (such as geographical distance from an expert provider), alternative interventions to ameliorate the negative psychosocial aspects of these conditions must be considered. In rare diseases, there is an increasing importance and presence of the patient as an active participant in their disease management and decisions (Aujoulat, Young, & Salmon, 2012; Aymé, Kole, & Groft; Black & Baker, 2011; Johnson, Kirschenbaum, Mason, & Rush, 2005; Polich, 2012). As such, this patient-centric focus calls for a parallel patient-centered research approach, such as interpretive phenomenological analysis (IPA) (Smith, Michie, Stephenson, & Quarrell, 2002). Before designing interventions, it is prudent to seek out the voice of the patient, and the qualitative component of this study affords that opportunity.

The proposed research is innovative because this is one of the first (likely the only) identified studies that explores perceived social isolation along with perceptions of availability of social support in rare diseases. In addition, the study will employ a mixed-methods approach whereby

the “voice of the patient” will be explored, via qualitative interviews, and findings from those interviews compared with the perceived social isolation scores on a quantitative instrument (validated in other adult populations, although not in rare diseases). The investigator’s preliminary experience with previous qualitative interviews of AATD and sarcoidosis patients suggests that individuals grappling with these rare conditions are eager and willing to give voice to their concern.

C. PRELIMINARY STUDIES

The investigator is a doctoral student in the College of Nursing at the Medical University of South Carolina, with a focus on the social burden of rare disease. Although not an academically funded researcher, she has an established industry track record of over 17 years of pharmaceutical clinical research experience, the last twelve in pulmonary research. For the past ten years, she has successfully led clinical teams in the design, execution and management of various early development studies, including two trials in the rare lung disease sarcoidosis, funded by her employer, and where she was an internal employee of the company. Over the past four years, she have successfully translated that experience and knowledge to doctoral studies, where formal coursework is concluding. As a doctoral student at the Medical University of South Carolina, she has been mentored in research involving rare disease populations under the tutelage of an experienced nurse scientist whose focus is also rare genetic conditions and a nurse scientist with expertise in community-based participatory research. The investigator also successfully completed an independent research project requiring travel to the EU, recruit, enroll and interview subjects for that project. As a result of her pharmaceutical and academic experiences, she is cognizant of the need to plan appropriately, execute precisely, and collaborate effectively and efficiently. In summary, the investigator possesses a demonstrated record of accomplished and productive research projects in an area of high relevance for our aging population, and her expertise and experience have prepared me to lead the proposed project.

D. RESEARCH DESIGN AND METHODS (including data analysis)

Overall Strategy. The mixed methods study design was informed by Creswell & Plano Clark (2011). Semi-structured, individual interviews will be conducted to provide phenomenologic data for thematic analysis (Braun & Clarke, 2006) to describe individuals’ perceptions of social support, relationships with others, and preferences for support strategies. A quantitative descriptive approach will involve participants’ completion of the Friendship Scale (Hawthorne, 2006), a six-item Guttman scale that measures social isolation and the Medical Outcomes Study: Social Support Survey (MOS-SSS), a 19 item version instrument that measures perceived availability of social support. A convergent design will allow the investigator to collect and analyze two independent data streams in a single phase (Creswell & Plano Clark, 2011). After merger, divergence, convergence and other relationships will be explored.

Sample Size Determination. Up to 275 participants will be enrolled in the trial, with the goal of an equal distribution of AATD and sarcoidosis participants. In this mixed-methods pilot study, all subjects will participate in the quantitative components and a subset (~30) will be requested to participate in the qualitative interviews, although the interviews are not a requirement. If a robust response is realized for the qualitative inquiry at the beginning of the study, the invitation for the interview may be temporarily halted in order to allow the investigator to interview those interested participants soon after their agreement to be interviewed. This size is robust for a pilot qualitative approach; other qualitative studies of rare disease participants have enrolled less than 20 per group (Bogart, Tickle-Degnen, & Joffe, 2012; Joachim & Acorn, 2003). Guidelines for sample size for studies using an interpretative phenomenological approach suggest that between 3-6 participants per group is reasonable; this provides sufficient cases for analysis without the risk of any overwhelming volume of data (Smith, Flowers, & Larkin, 2011). Other descriptive studies of

rare disease groups have typically included less than 50 participants (Anderson et al., 2013). Some researchers have also suggested that saturation in qualitative interviews may occur early. Guest, Bunce, & Johnson (2006) evaluated data from a study involving sixty in-depth interviews with women in two West African countries and documented the degree of data saturation and variability over the course of thematic analysis. They found saturation occurred within the first twelve interviews, and further, basic elements for themes appeared as early as after the first six interviews. Based upon the previous points, the proposed sample size is a reasonable goal.

The study will be introduced to potential subjects as a study that consists of two parts, an "interview" portion and a "questionnaire" portion. For the purposes of this study, caregivers will not be included as part of the study population. If subjects agree to participate in both parts, the preference is for the qualitative interview will be conducted first, followed by the quantitative component, but will be subject to participant availability and logistics. In this study, caregiver is defined as the individual who acts as a support person for the individual with the rare condition; typical examples include a spouse/partner, other relative or friend who provides physical and/or emotional support (Burns, et al, 2005).

- **Eligibility Criteria**
  - **Inclusion**
    - Participants will be eligible to participate in the study if they meet the following criteria:
      - Adult participants (male or female) ≥18 years of age
      - Self-report a physician diagnosis of AATD or sarcoidosis with pulmonary involvement
      - Self-reported ability to read and speak English
      - Have access to a computer with a valid email address (for purposes of completing instruments via REDCap)
  - **Exclusion**
    - Participants who self-report that they are caregivers, or have diagnoses other than AATD or sarcoidosis

For the purposes of presenting the research design and methods, each one of the three individual aims will be presented individually:

Aim #1: To explore perceptions of the social impact of living with rare disease by assessing perceptions of social isolation, social support, connectedness, social participation and relationships in adults with two rare lung diseases, AATD and sarcoidosis, in an academic center and/or via the Web using one-on-one interviews.
Introduction In rare diseases, it is critical to obtain the voice of the patient (Patsos, 2001). The objective of this aim is to elucidate individuals' perceptions of social isolation, social support, relationships with others, and preferences for support strategies. This approach has been used successfully in other studies investigating living with a rare disease (Feinberg et al., 2013; Joachim & Acorn, 2003; Vitale, 2005). To attain the objective of this aim, individual interviews will be conducted. The rationale for this aim is gather information related to individuals' experiences related to social support and social isolation, without imposing bias from predefined questions and/or categories.
Data Collection. For Aim #1, a semi-structured interview guide will be utilized for the purposes of conducting participant interviews. Interviews may take place in a face-to face setting, via phone, or via Skype® (or a similar web-based videoconferencing program). Following agreement to participate (via receipt of the Information for Survey Participants document) and during the interviews, the dialogue will be audio-recorded for the purposes of later transcription. For those subjects who may be participating via telephone or Skype® interviews, a script will be followed to ensure compliance to all verbal interview guidelines. This type of interview approach is based on a flexible topic guide that provides a loose structure of open ended questions to explore experiences and attitudes (Pope, van Royen, & Baker, 2002). In a hermeneutic approach to interviewing, the interviewer is the instrument and requires attention to the co-creation of the data

through the interaction between participant-respondent and interviewer (Lowes & Prowse, 2001). The interview script, comprised of eight questions, is designed to facilitate approximately 60-90 minutes of dialogue. The interviews will take place either face-to-face or via phone or Skype® for participants that are enrolled via the Internet.

This Heideggerian hermeneutic approach (Lowes & Prowse, 2001) will shape the interview and describe from a participant perspective, individuals' experiences in terms of living with a rare disease. Semi-structured questions and prompts are used to yield narratives centering on social isolation and/or social support ("tell me a little bit about the people you interact with during a typical day"; "tell me about who you could call on in times of need.). This approach will allow the researcher to utilize previous knowledge gained to guide the inquiry (Lopez & Willis, 2004).

Data Analysis: Interviews will be transcribed verbatim. The investigator will also maintain field notes to be used as a reference point and reflexive tool during data analysis. After conduct of and transcription of the interviews, all data will be uploaded into nVivo10. Following the guidelines prescribed by Smith et al., (2011), the investigator will seek immersion in the data by reading and re-reading each individual transcript. Initial coding will occur on an exploratory level, followed by a more refined review looking for emerging themes (Smith et al., 2011). Interview transcripts will be coded line-by-line and codes will be developed themes and subthemes, as suggested by (Braun & Clarke, 2006). After initial themes are identified, additional data abstraction will occur. Following this inductive approach, data will be revisited to see if any reorganization of categories or themes should occur (Creswell & Plano Clark, 2011). As an example of this approach, transcribed text that references support groups, online groups or advocacy involvement might code initially to a super-ordinate theme of "social support options". Themes will be summarized using frequencies and percentages. Data may be compared (between the two disease groups) using Fisher's exact test, in order to identify substantial differences in the responses between the two populations.

In addition, the number of attempted interviews compared with the number of completed interviews will be summarized.

Expected Outcomes. It is expected that participant interviews will yield information related to varying degrees of social support, perceived social isolation, and measures individuals have taken in the past to address their feelings. It is also expected that some subjects may not have taken any steps to address their feelings of being socially isolated. Analysis of themes is expected to generate inferences regarding the predominant themes in each sub-population, as well as the overall study population.

Potential Problems and Alternative Strategies. There are a number of potential problems that could arise as a result of the subjective nature of the qualitative approach. Difficulty establishing rapport with potential subjects could arise. For this particular study, the researcher will begin the interview with small talk and remind participants of their valuable contribution to the study. Social desirability is another form of bias that may be present. The population under study are both AATD and sarcoidosis participants who may suffer from the stigma of their disease, and may eagerly welcome the researcher's attention. As DiLorio suggests (2005) some individuals may respond in an optimizing or satisfying approach, or conversely, acquiesce and act as a naysayer (p 44). Qualitative research is prone to bias due to the inherent preconceptions and attitudes of the researcher (Hewitt-Taylor, 2001). Self-examination on the part of the researcher of their beliefs and attitudes can help to mitigate this risk.

Aim #2: To compare the Friendship Scale and the MOS-SSS in individuals who have ever accessed compared to never accessed a support group in Alpha-1 and Sarcoidosis. We will also evaluate these tools as measures of perceived social isolation and availability of social support, respectively.

Introduction. Pilot studies can be invaluable when assessing the feasibility of a planned design, the practicality of a given instrument, recruitment rates, and any data management issues that might occur, including response rates to questionnaires (Arain, Campbell, Cooper, & Lancaster, 2010; Thabane et al., 2010). This approach can be particularly useful when evaluating an existing instrument in a new population. Hawthorne (2006) suggests that when measuring social isolation in any population, brief scales that offer ease of administration and interpretation are

advantageous, such as the Friendship Scale. Response rates have been shown to be inversely correlated to questionnaire length (Edwards, Roberts, Sandercock, & Frost, 2004), although this relationship continues to be explored, and remains a topic of debate (Rolstad, Adler, & Rydén, 2011). The objective of this aim is to gain a sense of the magnitude of perceived social isolation and social support in the overall population, as well as within sarcoidosis and alpha-1 subjects. To attain the objective of this aim, subjects will be asked to complete the instruments via an electronic link to the REDCap site, where the instruments for the study will be located. Although the preference is for qualitative interviews to be completed prior to completion of the instruments, the timeframe of when subjects are available for interviews versus completion of the instruments may not support this preference. As such, subjects will be encouraged to complete the instruments at their convenience, irrespective of their willingness to participate in qualitative interviews. The rationale for this aim is that comparison and contrast of scores will provide valuable insights into the magnitude of perceived social isolation, and also assess the feasibility of the instruments in these populations.

Data Collection. For Aim #2, four instruments will be utilized for the quantitative component of the study: a general demographics questionnaire, the modified Medical Research Council (mMRC) Dyspnea Score (to characterize perceived breathlessness), an instrument to measure perceived social isolation (The Friendship Scale) and an instrument to measure perceived availability of functional support, the Medical Outcomes Study – Social Support Survey (MOS-SSS).

The *demographic instrument*, designed by the investigator, will collect information related to age, ethnicity, race, disability status, pain, fatigue, frequency of leaving the home, gender, marital status, living situation, income, years since diagnosis, condition, genotype (if AATD), disease severity (sarcoidosis), familial history of the respective condition, participation in support or advocacy groups (and the number of meetings attended) and participation in outside activities, by study population as a whole, as well as by disease condition (Appendix 6).

The second instrument is the *modified Medical Research Council (mMRC) Dyspnea Score*, a five item, standardized, self-administered scale to quantify the effects of breathlessness on everyday activities. The scale is used to document the impact of dyspnea on the subject's physical functioning. A 5 point scale uses statements about perceived breathlessness graded from 0 to 4 demonstrating increasingly severe loss of function (Bestall et al, 1999; Papiris et al, 2005). Dyspnea is rated in the present timeframe. The scale has been used successfully with subjects aged 6 to > 80 years (Darbee and Ohtake, 2006) with a completion time of approximately 5 minutes.

The third instrument is the *Friendship Scale*, a six-item Guttman scale that measures social isolation (Hawthorne, 2006). The psychometric properties of the scale in the validation study conducted in older adult populations living in various types of settings (nursing homes, hospital outpatients, older veterans, and community members) suggest that it has excellent internal structures as assessed by structural equation modeling (CFI = 0.99, RMSEA = 0.02), that it possesses reliability (Cronbach's alpha = 0.83), and discrimination when assessed against two other short social relationship scales (Hawthorne, 2006; Hawthorne, de Morton, & Kent, 2013; Nikmat, Hawthorne, & Al-Mashoor, 2013). A subsequent validation study in individuals with low back pain showed similar results (Hawthorne et al., 2013). The scale has been used in a study of over 3,000 community-dwelling residents of Australia, ranging in age from adolescence to the elderly. Use of the Friendship Scale in any rare disease population has not been identified in the published literature. However, the consistent psychometric results of the scale in diverse populations suggest that the scale may possess similar validity in the populations under consideration, although this needs to be explored.

Tests of concurrent discriminant validity suggest it is sensitive to the known correlates of social isolation (Hawthorne, 2006). The scale covers both critical aspects of social isolation: perceived social isolation and perceived emotional loneliness. Three of the six items assess perceived

social isolation and the other three assess perceived loneliness. Scores for each item range from zero to 4; an individual's total score on the instrument can range from zero to 24. Scoring is by simple summation. Cutpoints to classify different levels of social isolation are as follows:

- 0-11: Very socially isolated
- 12-15: Isolated or with a low level of social support
- 16-18: Some social isolation or some social support
- 19-21: Socially connected
- 22-24: Very or highly socially connected (Hawthorne, 2006).

Finally, the fourth instrument is the *Medical Outcomes Study: Social Support Survey (MOS-SSS*). This is a 19 item version instrument that measures perceived availability of social support. It contains four domains to assess perceived availability of social support, including (1) emotional/ informational support, (2) tangible support, (3) positive social interaction and (4) affectionate support (Sherbourne & Stewart, 1991). Responses are given by the subject using a 5 point Likert-type scale, and range from "none of the time" to "all of the time". Scores range from 0-100 with higher scores indicating more perceived support. The MOS-SSS has been utilized extensively in various populations (Carod-Artal, Ferreira Coral, Trizotto, & Menezes Moreira, 2009; Cuijpers, 2001; Duncan et al., 1997; Sherbourne & Stewart, 1991), and more recently, in studies of social support in COPD patients (Zijing et al., 2014)

All instruments will be completed by the subjects, at a time convenient to them and accessed via an electronic link sent to them via email.

Power Analysis

The sample size calculation is based upon the Friendship Scale. In the general population, the mean total score for the Friendship Scale was 21 (SD 3.47) (Hawthorne, 2006)(We hypothesize that the total Friendship scale score reflecting social connectedness for the entire study population is 20 representing a difference in total scores of 1 point on the Friendship scale. To have 80% power to detect a difference of 1 point in total scores between the general population and the study sample of alpha-1 and sarcoidosis patients, assuming a common standard deviation of 4.0 for alpha=0.025 (one-tailed test), 126 subjects are required. The assumption of a lower score for the disease groups under study is based upon references in the literature which suggest some degree of social isolation in these individuals (Colledge & Solly, 2012), although that has not been formally tested. For further comparison of social connectedness between the two disease subgroups (alpha-1 versus sarcoidosis) with 60 participants per group we will have 80% power to detect a two point difference in total Friendship scores between the groups assuming a common standard deviation of 4.0 for a two-tailed t-test (alpha=0.05).

Data Analysis:

Subjects will complete the questionnaires in REDCap. Data from REDCap will be exported to SPSSv22 for analyses.

- **Descriptive statistics** will be computed on the demographic and clinical characteristics of the study population.
    - Where appropriate, and for categorical variables including ethnicity, race, gender, marital status, living situation, income, disease condition, genotype (if AATD) or staging (if sarcoidosis) activities, participation in support groups, hearing and sight status, and challenges with stair climbing and/or dressing or errands, frequencies (both absolute and relative) will be reported for each item.
    - For ordinal variables, such as years since diagnosis and income, frequencies (absolute and relative) will be reported.
    - For the continuous variables of age, number of years since diagnosis, pain and fatigue day counts, and days that the subject has left their house, measures of central tendency including mean, median and standard deviation will be reported.

- Disease groups will be compared with respect to their demographic and clinical characteristics using t-test and chi-square tests as appropriate for continuous and categorical variables, respectively. If non-normality is observed appropriate non-parametric tests will be used instead.
- **Feasibility** of the instruments will be examined by assessing recruitment rates, completion rates and time to completion. Participants will be asked to rate both instruments in regard to ease of completion (very easy to complete/easy to complete/hard to complete/very hard to complete) (see Appendix 5).
    - **Recruitment patterns** will be examined
        - Numbers of potentially eligible subjects versus number who consent to participation will be reported as proportions
            - Number of completed instruments versus number of attempted instruments will be reported using proportions.
            - A "completed" instrument is defined as an instrument where >90% of the items have been responded to by the subject.
                - For the Friendship Scale, the subject will enter a response to the 6 questions
                - For the MOS-SSS, the subject will enter a response to the 19 items
            - For those instruments with missing scores, missing values will be assumed to be missing at random, and imputed using the Individual mean imputation approach.
                - The imputed value is the calculated mean of a given subject's complete responses to other questions. If a participant has 2 missing responses, the values are filled with the calculated average of the remaining completed 18 questions (Shrive, Stuart, Quan, Ghali, 2006).
    - **Faciliators and barriers to recruitment** will be examined in anticipation of their impact on subsequent trials
        - Use of patient advocacy contacts, clinician-experts, social media outreach will be considered and reported as well as the number of enrolled participants that come from these various methods
        - For those subjects who participate in the qualitative portion of the study, prompts will explore the reasons for participation.
- **Differences between completion rates** will also be examined.
    - Completion rates will be summarized and compared using an ANCOVA model by ease of completion (easy/not easy), mode of delivery ('live" versus electronic) and disease population (sarcoidosis / alpha-1)
        - The Kruskal-Wallis test will be used to compare completion rates by income level. Chi-square, df and significance will be reported
    - Ease of completion will be summarized and compared using the Cochran–Mantel–Haenszel test, stratifying on income and disease.
- **Reliability**
    - Reliability will be explored by calculating Cronbach's alpha for the overall population and each disease population. For the Friendship Scale, a will be reported for the overall scale. For the MOS-SSS, a will be reported for both the subscales as well as the overall instrument.
- **Validity**
    - **Content validity** will be assessed by presenting the two scales to three experts in the field prior to having any subjects complete the questionnaires: (1) a sarcoidosis expert, (2) an alpha-1 antitryspin deficiency expert and (3) an expert in the area of instrument development. Although not expert in the field of patient-reported outcomes, the scales will be presented to two expert, disease-specific clinicians to assess clinical relevance.
    - **Concurrent validity** will not be explored at this time due to the limitations of the study size and time.

- **Convergent validity** will be explored by correlating scores on the Friendship Scale with scores on the MOS-SSS; it is hypothesized that higher Friendship Scale scores will correlate to lower MOS-SSS scores (indicating less perceived support).

- **Social isolation and social support scores:**
- For the Friendship Scale, negatively worded items (items 1, 3 and 4) will be reverse scored so that their valence matches the positively worded items (Hawthorne, 2006).
- For the MOS-SSS, scores for each subscale will be obtained by
  - First, individually calculating the average of the scores across all respective items in each subscale.
  - An overall support index will be calculated by summing the average of
    - the scores for all 18 items included in the four subscales, and
    - the score for the last item of the scale, which asks the subject if they have "someone to help them keep their mind off of things". This last item is not included in the 4 subscales
  - Finally, scores will be transformed to a range of 0 to 100 using the developers' instructions and the following formula (Sherbourne and Stewart, 1991):

$$\frac{100x(observed\ score - minimal\ possible\ score)}{(maximum\ possible\ score - minimal\ possible\ score)}$$

- Mean total scores (with 95% CIs) will be calculated for the pooled study population (alpha-1 and sarcoidosis subjects) for both the Friendship Scale and MOS-SSS.
  - Subsequently mean total scores (with 95% CIs) will be calculated for the individual disease groups for both scales. The mean scores of each disease ;)
  - group will be compared with the mean score for the overall study population.
  - The pooled study population will be dichotomized into individuals who have accessed online or face-to-face support groups and those who have not accessed such groups.
    - We will compare mean total scores (with their 95% CIs) for both the Friendship Scale and MOS-SSS to determine if there is a difference between the groups of subjects who have accessed compared to not accessed online or face-to face support groups. ,
    - In addition we will compare the means for these tow groups stratified for disease state. Independent t-tests will be used to examine the differences in the Friendship Scale and MOS-SSS scores between individuals who have accessed online or face-to-face support groups and those who have not.
    - Results will include the t-statistic, the *df*, and the degree of significance.
    - If non-normality is observed, alternatively, Wilcoxon rank-sum tests will be utilized to examine the difference in the Friendship Scale and MOS-SSS scores between individuals who report access to online or face-to-face support groups.
      - Results will include W, the z-score and the significance level, along with the median score. Mean scores (and SDs) will also be reported, if careful consideration of outliers merits inclusion of the value.
- Exploratory logistic regression will be used to determine whether any of the demographic or clinical characteristics might be predictive of higher/lower social isolation or social support scores.
  - The Friendship Scale will be dichotomized into those who were very isolated, isolated, and with some isolation [range of scores 0-18] versus the socially connected and very socially connected [range of scores 19-24]) (Hawthorne, de Morton, & Kent, P. (2013).

    - The MOS-SSS will be dichotomized to indicate those who perceive low-normal social support (below 75th percentile) or high social support (above or equal to the 75th percentile) (Sherbourne, Meredith, Rogers and Ware,(1992).
- Odds ratios (with 95% CIs) for each predictor will be calculated and presented. Of particular interest are age, sex, race, education level, pain scores, and disease severity indices.
    - Missing values will be assumed to be missing at random, and will be imputed using the multiple imputation procedure available in SPSS.

95% confidence intervals will be calculated and presented to provide measures of precision of the outcome estimates.

Expected Outcomes. It is expected that the analyses of the quantitative scores will generate inferences regarding the magnitude of perceived social isolation in each sub-population, as well as the overall population. There may also be some outlier scores; these scores will be examined individually, as well as in the context of the individuals who completed those respective instruments.

Potential Problems and Alternative Strategies. The expectation is that participants in the overall population will report some degree of social isolation, as measured by the Friendship Scale. The literature review, albeit brief, supports this expectation. However, there is the remote possibility that this is not the case, and that some subjects do not report perceptions of social isolation. In that event, the demographic questionnaire and qualitative interviews would be reviewed for confirmation of participation in support groups, advocacy efforts and/or strong family/friend support. These potentially confounding variables could also explain why some individuals do not report perception of isolation.

Various measurement errors can occur with the use of the Friendship Scale. Random error can occur because of noise or distraction and as a result, the participant enters incorrect responses. Idiosyncratic error also is possible, since three of the item responses are reversed. It is possible that participants could indicate the wrong response due to the preceding response. The potential for social desirability response bias exists, in that participants might provide responses for which they think that the researcher will approve. To mitigate this risk, the researcher will sit quietly with each participant, allow a dialogue to occur, and remind them that the researcher is not there to judge, but to collect the most precise data possible. “Faking bad” occurs when a participant answers in a more negative manner because they think that they might benefit from it (Di Lorio, 2005). The researcher has included information in the Information for Survey Participants form that details the expectations of the participant and the consequences of participating in this research study. The Friendship Scale has a 4-week recall period. This can be challenging, especially if the participant responds quickly to the question, rather than considering the recall period (Di Lorio, 2005). One way to mitigate this would be to conduct cognitive interviews to understand what participants are thinking as they respond to the questions (Nápoles-Springer, Santoyo-Olsson, O'Brien, & Stewart, 2006). However, this would not be optimal in this case due to the time constraints of the current study. The researcher will remind each participant of the 4-week recall period prior to the participant completing the scale. The scale is self-administered by the participant. As DiLorio (2005) suggests, an introductory cover letter may help to ameliorate incorrect responses, by helping to focus the participant and put them in the proper frame of mind. Environmental factors that could cause measurement error could be an overcrowded room, where the participant might not be comfortable (for the face-to-face cohort) or lack of familiarity with the computer (for the web-based cohort).

Aim #3: Triangulate the survey and interview results to identify areas for development of interventions and preferences to improve individuals’ preferred level of social interaction.

Introduction. Triangulation of data can enhance completeness and trustworthiness of the work, in addition to providing for a more in-depth analysis of the findings. The approach of combining closed-ended questionnaires, like the Friendship Scale, with qualitative interviews, such as the one proposed, is one of the most common mixed-methods approaches in the literature (Creswell & Plano Clark, 2011). As this parallel, convergent, mixed-methods design is intended to be exploratory in nature, the objective of the triangulation of data from both the quantitative and qualitative strands is to combine or link the findings into meta-inferences of the study findings as a whole (Teddlie & Tashakkori, 2009). To attain the objective of this aim, after concurrent data collection, both data streams will be independently analyzed. Based upon the findings, specific dimensions will then be identified on which to compare the findings (Creswell & Plano Clark, 2011). The rationale for this aim is that subjective narratives may identify areas for further item development not captured in the Friendship Scale and provide insights into intervention development. When the triangulation of data is completed, it is the investigator's expectation that the results will yield information to provide for further refinement of subsequent larger studies, with an eye towards identification of possible strategies that can ameliorate perceived social isolation.

Triangulation:
This project combines qualitative and quantitative data from multiple data sources to support a preliminary, yet comprehensive evaluation of the perceived social impact of living with a rare disease. Triangulation of data and methods provides a more holistic and contextual representation of the phenomenon under investigation, and reveals the varied dimensions of the phenomenon, with each source contributing an additional piece to the puzzle. In using triangulation, bias can be minimized and validity enhanced.

In this study, the investigator will implement the process of conceptual triangulation described by (Foster, 1997). Conceptual triangulation involves "a search for logical patterns of relationship and meanings between the variables measured by either or both qualitative and quantitative methods." (Mitchell, 1986, p25) This process is designed to achieve a more complete and contextual portrayal of the phenomenon of interest. The process of conceptual triangulation involves five steps: 1. conducting qualitative and quantitative research true to the paradigmatic assumptions of each methods,2. distinguishing pertinent results within each methods, 3. examining confidence in the results, 4. developing criteria for inclusion of results in the conceptual model, and 5. constructing one or more preliminary conceptual models of the social impact of a rare disease. Due to the limitations of this dissertation study (sample size, study populations, time and budget constraints), the development of such a model may not be possible, but will be considered throughout all phases of the research process.

Research Design. Following completion of Aims #1 and #2, data will be compiled for triangulation. The matrix below presents the **planned triangulation strategy:**

Method Data Collection	Type of Triangulation	Method of Analysis	Purpose/Goal
Qualitative	**Within Method**		
Subject Interviews	Investigator	Audio-recorded, , transcribed, analyzed for themes	Deepening understanding of subjective experiences
Field notes	Investigator	Analysis of text	Document observations, scenarios, not easily interpreted from text
Quantitative	Between Method		
Friendship Scale MOS-SSS mMRC-Dyspnea	Data	SPSSv22; descriptive analyses; inferential analysis using non-parametric statistical tests; chi-square analysis, exploratory logistic regression	Triangulation of qualitative data with results of the scale to determine if interview findings are reflected in scale scores

As data will have been reviewed separately for Aim #1 and Aim #2, this third Aim will employ revisiting the data as a whole, to assess for convergence of divergence of findings.

Expected Outcomes. This is the first known mixed methods study to explore any psychosocial phenomenon in rare disease patients. It is anticipated that the results may reveal some degree of social isolation in both groups, and the isolation may be directly correlated with disease severity (more severe disease equates to increased perceived social isolation). Phenomenological findings may add rich information regarding the characteristics of perceived social isolation that cannot be measured with the Friendship Scale. In addition, it is anticipated that qualitative responses detailing participants' previous experiences with support groups or activities will inform future studies designed to investigate various interventions. Themes that reflect coping with or decreasing social isolation will be used in hypothesis generation and a later process of intervention mapping (Kok, Schaalma, Ruiter, van Empelen, & Brug, 2004). Inferences from the QUAN and QUAL datastreams will inform meta-inferences for the overall study.

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

Human participants affected by rare lung diseases can experience a number of various psychosocial challenges related to their rare disease, including perceptions of social isolation. The cause of these perceptions is the topic of this proposed research. Approximately 275 human participants (with the goal of enrolling an equal number of sarcoidosis and alpha-1 subjects) will be invited to take part in this study to assess and compare perceptions of social isolation. Human participants will take part in individual interviews as well as completion of a short, quantitative questionnaire. The investigator will be the sole individual conducting the interviews and administering the questionnaire at a single time point. Interviews are planned to be conducted face-to-face; however, telephone or Skype interviews may be utilized.

Subject Population Characteristics. The collaborating academic institution, the Medical University of South Carolina, is a large academic institution with established clinics that serve a large population of alpha-1 and sarcoidosis patients, respectively. The investigator has established previous academic relationships with the collaborating physician, Dr. Charlie Strange (MUSC). The Alpha-1 Research Registry, located at MUSC, has currently enrolled over 3300 individuals with Alpha-1 Antitrypsin Deficiency (Alpha-1 or AAT Deficiency) or a carrier phenotype willing to participate in Alpha-1 research. The Registry was established in 1996 by the Alpha-1 Foundation in accordance with recommendations of the World Health Organization, to facilitate research initiatives and promote the development of improved treatments for Alpha-1 Web-based

support groups that the investigator belongs to, (including the Alpha-1 support group and the Sarcoidosis Online Sites groups) have more than 600 and 1800 members, respectively. In addition, subjects may be recruited via postings on the NORD (National Organization for Rare Disorders) and INSPIRE (an online community for individuals with rare conditions) websites. It is anticipated that the average age will be 50 years, ~60% female, ~40% male, approximately 40% black (primarily driven by the sarcoidosis population), 60% white.

We anticipate <1% of the population will be Hispanic, which reflects the ethnic make-up of the recruitment area. We will include English-speaking participants only due to the pilot nature of the study, limited resources and the special needs of bilingual and culturally sensitive protocol/materials. Children will not be included as sarcoidosis is generally limited to adults, and alpha-1 antitrypsin deficiency with lung involvement is also very rarely identified in children.

Targeted/Planned Enrollment Table

Total Planned Enrollment 275

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
	Sex/Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	2	3	5
Not Hispanic or Latino	200	70	270
Ethnic Category: Total of All Subjects*			
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	50	50	100
White	110	65	175
Racial Categories: Total of All Subjects*	160	115	275

b. Sources of Materials

Materials obtained from the participants include questionnaires and interviews. Demographic data includes information related to age, ethnicity, race, disability status, pain, fatigue, gender, marital status, living situation, income, years since diagnosis, condition, genotype (if AATD), disease severity (sarcoidosis), familial history of the respective condition, participation in support or advocacy groups (and the number of meetings attended) and participation in outside activities, by study population as a whole, as well as by disease condition (Appendix 7). These data will be collected from interviews by the investigator to further characterize and describe the sample. The questionnaires (demography, the Friendship Scale, the MOS-SSS, and the mMRC Dyspnea Scale) can be done in less than 30 minutes to reduce participant fatigue and burden. Participants will enter their own data into REDCap via an electronic link sent to each participant via email. Access to the REDCap database will be given to the investigator's advisor.

c. Potential Risks

There are potential risks inherent to any type of interview approach such as psychosocial impact and increased focus on the negative aspects of any condition. There is minimal risk to the participants in terms of acute injury as no interventions will be performed. Consenting

participants will respond to interview, demographic and scale questions as described above. Breach of confidentiality is a potential risk. It is possible that individuals familiar with study subjects at a particular research site could identify those subjects who participate in this study. Personal identifying information will not be stored with data.

F. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Recruitment. Access to participants will be facilitated through an established relationship with a clinician expert located at the Medical University of South Carolina. In addition, the investigator has established a network of patient contacts who participate in Web-based support groups (such as www.Inspire.com and NORD (National Organization for Rare Disorders (www.rarediseases.org) and other rare disease initiatives. Representatives from these organizations have been contacted and are amenable to posting notification of the study on their Web pages and/or Facebook pages. Prior to study commencement, these individuals have been contacted and informed about the study with the intent of collaborating with them as a source of potential participants. Web-based recruitment may be utilized to enroll a portion of the participants in the study. In rare disease research, the internet has been a key and expanding method for recruiting clinical study participants and publicizing new studies and/or areas of focus (Griggs et al., 2009; Schumacher et al., 2014).

Informed Consent

The study seeks a waiver of informed consent, since no interventions are being performed. Subjects may be accessed via the following avenues:

- Dr. Charlie Strange at MUSC
- The Inspire website,
- The NORD Facebook page
- Via previous patient contacts known to the investigator, including patient support groups.

Study Procedures

All potentially interested subjects will be provided with the email and phone number of the investigator.

- They will be asked to contact the investigator for further information, and to provide their first name, last initial, contact email and phone number.
- For these subjects, a prenotice letter will be sent (via email) that acquaints them with the study and explains the purpose of the current data collection.
    - A second follow-up email contact and a follow-up phone call (where possible) will be used to bolster participation of those who do not respond to the initial mailing.
- The prenotice letter will be followed with by an email containing an electronic link directing them to the REDCap link which will include an *Information for Survey Participants* document, a patient information module (requesting first name, last initial, phone number, email and the electronic versions of the instruments.

Quantitative Procedures (REDCap Survey)

- Once entering the REDCap site, the first module that the subjects will see is the *Participant Information Survey* (5 items), which collects the first name, last initial, email address and phone number.
    - In addition, the last question in the *Participant Information Survey* section of the REDCap site asks the subjects specifically if they would be willing to participate in the qualitative interview.
    - *"Would you be willing to participate in a short (30 minute) interview with the investigator, in addition to responding to the surveys here?"*
    - *If the participant responds yes:*

        - They can continue through the REDCap site, complete the survey/instruments, and be contacted by the investigator to determine a mutually agreeable time to be interviewed
        - Alternatively, the can opt to complete the interview prior to completing the surveys.
            - Both options are at the discretion of the subject, and intended to decrease respondent burden
            - The investigator receives notification when a new subject has accessed the REDCap site, and so will be made aware of any new/potential participants
        - If the interview is conducted in person, it may be conducted either at the MUSC clinic site of Dr. Strange, or at a mutually agreeable location (for both subject and investigator) if the participant is local to the investigator.
        - The interview will be audio-recorded and transcribed at a later date for purposes of qualitative coding and analysis.
        - No protected health information (PHI) will be collected, other than the participant's first name, last initial, and diagnosis.
    - If the participant responds "no"
        - They can continue through and complete the online surveys.

- The next module that the subjects will complete is the *Demography* module (26 items), which asks questions about the subject's age, race, levels of pain, fatigue, impairments of hearing, vision, concentration, mobility, ability to perform activities of daily living, gender, marital and living situation status, levels of income and education, disease and duration of condition, participation in support groups and other activities.
- The third module that the subjects will complete is the *modified Medical Research Council (mMRC) Dyspnea Scale*, a 5 item scale that asks the subject about their level of perceived dyspnea
- The fourth module is the *Friendship Scale,* a 6 item scale that inquires about the subject's perceptions of social isolation
- The fifth module, the *Medical Outcomes Study: Social Support Survey (MOS-SSS*), is a 19 item instrument that measures perceived availability of social support. It contains four domains to assess perceived availability of social support, including (1) emotional/ informational support, (2) tangible support, (3) positive social interaction and (4) affectionate support
- Subjects will be asked about the ease of completion for both the *Friendship Scale* and the *(MOS-SSS*), by ranking the level of difficulty from "very easy to complete" to "very hard to complete"

Qualitative Interview

Although it is preferable for subjects to be interviewed prior to completing any of the instruments, in order to minimize bias that the instruments may impose, it is likely that subject interviews may take place after respective subjects complete the surveys. Approximately 30 subjects will be interviewed. Measurement generation will begin by collecting a range of patient perspectives regarding feelings of social isolation and social support. Interviews will be facilitated by a semi-structured interview guide, allowing opportunity for interviewees to share additional experiences not addressed by the questions.

Location/Duration/Approach of Individual qualitative interviews The investigator will be the sole conductor of the individual semi structured qualitative interviews; following a prepared topic guide. It is anticipated that 30 subject interviews will allow for saturation of the topics of social isolation and social support. Interviews will be audiotaped at the time of conduct. Interviews will be conducted in person, via telephone conference or virtually (ie, Skype®), depending upon logistics.

Following completion of the subject interviews, all information will be transcribed and uploaded into nVivo for further qualitative analysis.

As we are requesting a waiver of signed consent, this *Information for Survey Participants - Statement of Research* document will be provided and it will describe the goals of this study and will contain all other required elements of consent. It also notes what will be asked, how long it should take to complete, assurance of confidentiality, and that remuneration - in the form of entry into a drawing for an Apple iPad – is optional for participants. Participants will be informed that consent to participate is implied by return of the completed survey.

b. Protection against Risk

Minimal risk is anticipated. In the event of an unexpected event as a result of participating in the interviews, the participant will be instructed to contact the investigator. Based on the experience of the PI, it is anticipated that the risk of AEs will be acceptably low. In the event of an AE, it will be recorded and submitted to the IRB and PI according to institutional procedures. The PI and PI's doctoral advisor will review all AEs.

The Information for Survey Participants document assures confidentiality of all information obtained during the study. In particular, confidentiality of subjects will be guarded by conducting data collection (interviews and questionnaire instrument administration) in a private clinical setting/location that will be secured by the investigator in advance of the planned meeting. The confidential data will be deidentified for purposes of transcription and analysis. Each subject will be assigned a unique participant code known only to the investigator and maintained in a locked fashion. Breach of confidentiality may be considered an adverse event, and may be reported to the IRB. Maximal efforts will be undertaken to ensure the safety of all participants. Participants will be instructed on how to access the, PI or in the event of study-related questions. In the event of study-related illness or injury, participants will be instructed on how to access health care. Participants will be given a card with the investigator's name and phone numbers to contact in the event there is a problem.

All personal information, such as phone numbers or emails for follow up, will not be connected to any data and will be discarded after interviews are complete and the Apple iPad is distributed. Each subject will be assigned a unique study ID number for the purposes of linking a unique person with a given set of data.

There are no social or legal risks associated with participation in the study. Confidentiality will be maintained for all other collected data. The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no paper copies will be made. All reports and communications relating to the study will identify subjects by assigned number. All electronic files will be protected via encryption, and the password(s) to those files accessible to the investigator and the investigator's doctoral advisor only.

G. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

There is no direct benefit of the research to the subject. However, the disclosures of the participants will inform future measurement of perceptions of social isolation and other social burdens not yet recognized or addressed by the scientific community. Measurement develops empirical evidence to support intervention development and identify health disparities.

H. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study will provide valuable information for the purposes of informing future studies designed to investigate interventions that can ameliorate social isolation in individuals with Alpha-1 antitrypsin deficiency, sarcoidosis, and potentially other rare lung diseases. In addition, the knowledge gained is important because these sample communities could be representative of the needs of other rare disease populations

I. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

N/A

J. REFERENCES/LITERATURE CITATIONS

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G.CONSULTANTS

Where applicable, attach electronic versions of appropriate letters from all individuals confirming their roles in the project. Go to the application under "additional uploads" to attach this information.

N/A

H. FACILITIES AVAILABLE

Describe the facilities available for this project including laboratories, clinical resources, etc.

N/A

I. INVESTIGATOR BROCHURE

If applicable, attach the electronic version of the investigator brochure. Go to the application under "additional uploads" to attach this information.

N/A

J.APPENDIX

Attach any additional information pertinent to the application, such as surveys or questionnaires, diaries or logs, etc. Go to the application under "additional uploads" to attach this information.

Uploaded as separate, individual attachments in eIRB.

Table 8. Triangulation of quantitative and qualitative findings.

Domain	Quantitative Instrument Scores Overall Population	Quantitative Instrument Scores Alpha-1 Population	Quantitative Instrument Scores: Sarcoidosis	Qualitative Narratives: Alpha-1	Qualitative Narratives: Sarcoidosis
Social Support ***[as measured by the MOS-SSS Total Score]***	63.8 (some lack of support)	66.4 (some lack of support)	56.9 (more pronounced lack of support)	• "And my kids they are not very sympathetic; there is no real empathy there from kids. They know I have this problem but they really are not too interested or involved." [FS 4; MOS-SSS 1.3] • "I couldn't be happier with the Alpha-1 support system that is in place. I have just involved, I am going to be involved in a study in St. Louis for the liver."[FS 24; MOS: 96.1] • "There is no support group where I live. It's like two hours away. I do have good support… I do a lot of online."[FS 18; MOS: 64.5]	• "I am on the two Facebook pages… But to be honest with you I try to stay off those because I get depressed because there's people in worse condition than I am"[FS: 23; MOS: 96.1 • "I am also a member of the Peer Support Unit of Boston Police Department even though I am retired, and we've got resources there that I can call, contact you know I can contact and call upon if I need support." "[FS: 23; MOS: 96.1] • "I feel fortunate that I have that, and like I said the biggest thing for me with the, was the Facebook pages…social media can be a good thing… just when I look at people that are worse off than me I am like this really isn't for me" [FS: 23; MOS: 96.1] • "I have some friends on Facebook … I can talk freely to and I feel– … they tend to be judgmental or they tend to just, I am sicker than you and I am this, there is a lot of "I" going around, I don't like a lot of the groups on Facebook, so I have five or six people that I talk to regularly."[FS: 15; MOS:

Table 8. Triangulation of quantitative and qualitative findings.

Domain	Quantitative Instrument Scores Overall Population	Quantitative Instrument Scores Alpha-1 Population	Quantitative Instrument Scores: Sarcoidosis	Qualitative Narratives: Alpha-1	Qualitative Narratives: Sarcoidosis
				good support – the only thing that I miss is being able to have somebody go, yeah, I totally understand, but much you may know me the side of the other thing."{FS 18; MOS: 64.47] • "I'm on Facebook and I have got hundreds of friends on Facebook and they all seem to know that I have this double thing going on. I don't care, I'm open about it. It's how I get my support"[FS 17; MOS: 64.47]	and there are only five people in my support group and in January nobody came to my meeting, I had a guest speaker, so totally embarrassed that nobody came…I want to just to reach out to everybody and like, are you going to come if I have a meeting because I don't want to come and sit there by myself for an hour." [FS: 15; MOS: 35.5] • "..The XX site has gotten a pretty unhealthy lately. So we pulled off about eight months ago and said let's create the little Facebook group and private group. This little tight group is seven of us who always seem to respond to each other's post and always seem to be very supportive of each other just had to make a little offset group…" [FS: 15; MOS: 35.5]
Social Isolation ***[as measured by the Friendship Scale]***	16.3 (some social isolation or some social support)	17.0 (some social isolation or some social support)	14.5 (isolated or with a low level of social support) ** *findings between alpha-1*	• "I have a very small core support group of family and friends that know my condition that I feel comfortable being around because they know why I am slow,	• "…. support is very important, you do feel very isolated with this disease..there is not a lot out there. There is not a lot of medical information out there." [FS: 15; MOS: 35.5] • "I have some [friends] that talk to me on Facebook; for the most part my friends have

Table 8. Triangulation of quantitative and qualitative findings.

Domain	Quantitative Instrument Scores Overall Population	Quantitative Instrument Scores Alpha-1 Population	Quantitative Instrument Scores: Sarcoidosis	Qualitative Narratives: Alpha-1	Qualitative Narratives: Sarcoidosis
			population and sarcoidosis population were statistically significant at p=0.009	why I get short of breath. But mostly I don't have a social life anymore"[FS: 14.4; MOS: 81.6] • "I still go as much as I feel that I can, I still isolate myself more than average person probably that's much better than what I want to do."[FS 9; MOS: 13.2] • "Let me tell you what I call this disease. I called it the lonely disease and that probably sums it up in a nutshell." • "Mine (life) has been impacted negatively very much and I know and it gets a little bit or it gets more isolated you know as time goes by". [FS 17: MOS:	gone; I don't have the common things that we used to working together." [FS 7; MOS 11.8] • "I didn't talk to people for months on end because it was just so depleting to even have a talk"[FS 20; MOS: 89.5] • "I'm rarely out instead of rarely in the house, now I'm rarely out of the house. I am very much -- I almost feel hermitish, because I know that if I -- even if I do feel good and I go and do one of those things, I will have trouble for the next two days after that with pain"[FS 15; MOS:61.8] • Mostly there are days that are so lonely and so – just – that I have actually said to my physician I promise you I cannot live the rest of my life this way and I meant every ounce of the word.[FS: 20; 96.1]

Table 8. Triangulation of quantitative and qualitative findings.					
Domain	**Quantitative Instrument Scores Overall Population**	**Quantitative Instrument Scores Alpha-1 Population**	**Quantitative Instrument Scores: Sarcoidosis**	**Qualitative Narratives: Alpha-1**	**Qualitative Narratives: Sarcoidosis**
				64.5]	